DRAFT
TOXICOLOGICAL PROFILE FOR
1,4-DIOXANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
Mail Stop F-32
Atlanta, Georgia 30333

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792) and October 25, 2001 (66 FR 54014) . Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Sharon Wilbur, M.A.
Dennis Jones, D.V.M.
Scott Wright. M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Fernando Llados, Ph.D
Mark Osier, Ph.D
Gary Diamond, Ph.D
Richard Amata, M.S.
Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for 1,4-dioxane. The panel consisted of the following members:

1. Dr. George Alexeeff, Deputy Director for Scientific Affairs, Office of Environmental Health Hazard Assessment, CAL/EPA, Walnut Creek, California;

2. Dr. Phillip Leber, Consultant in Toxicology, Akron, Ohio; and

3. Dr. Raghubir Sharma, Fred C. Davison Distinguished Chair in Toxicology, Department of Physiology and Pharmacology, University of Georgia College of Veterinary Medicine, Athens, Georgia.

These experts collectively have knowledge of 1,4-dioxane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about 1,4-dioxane and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. EPA then places these sites on the National Priorities List (NPL) and targets them for federal long-term cleanup activities. 1,4-Dioxane has been found in at least 27 of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the number of sites at which 1,4-dioxane is found could increase as more sites are evaluated. This information is important because these sites may be sources of exposure, and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you contact it—by breathing, eating, or drinking the substance or by skin contact.

Many factors determine whether exposure to 1,4-dioxane will harm you. These factors include the dose (how much), the duration (how long), and the way you contact it. You also must consider any other chemicals to which you are exposed and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS 1,4-DIOXANE?

1,4-Dioxane is clear liquid that dissolves in water at all concentrations. It is used primarily as a solvent in the manufacture of chemicals and as a laboratory reagent; 1,4-dioxane also has various other uses that take advantage of its solvent properties. 1,4-Dioxane is a trace contaminant of some chemicals used in cosmetics, detergents, and shampoos. However, manufacturers now reduce 1,4-dioxane from these chemicals to low levels before these chemicals are made into products used in the home.

1.2 WHAT HAPPENS TO 1,4-DIOXANE WHEN IT ENTERS THE ENVIRONMENT?

1,4-Dioxane can be released into the air, water, and soil at places where it is produced or used as a solvent. In air, 1,4-dioxane is present as a vapor. It does not react directly with sunlight. However, in the atmosphere, sunlight can form reactive compounds that can change 1,4-dioxane into different compounds. In water, 1,4-dioxane is stable and does not degrade; therefore, fish and plants will not accumulate it in their tissues. In soil, 1,4-dioxane does not stick to soil particles, so it can move from soil into groundwater. For more information, see Chapters 4, 5, and 6.

1.3 HOW MIGHT I BE EXPOSED TO 1,4-DIOXANE?

You can be exposed to 1,4-dioxane when you breath air, eat food, or drink water contaminated with it. However, current levels of 1,4-dioxane in air, drinking water, and food samples are unknown. In the mid 1980s, levels of 1,4-dioxane in outdoor air ranged from 0.1 to 0.4 $\mu g/m^3$ (or 1–4 10 millionths of a gram of 1,4-dioxane per 1 cubic meter of air). Levels in outdoor air also can be expressed as 0.03–0.11 parts per billion in units of volume (or ppbv). For indoor air, the average concentrations of 1,4-dioxane were 10 times higher than in outdoor air at levels of 4 $\mu g/m^3$ (or 4 millionths of 1 gram of 1,4-dioxane per 1 cubic meter of air). Levels in indoor air also can be expressed as ppbv. In the 1970s, drinking water sampled in the United States reportedly contained 1 µg/L (1 µg/L is 1 millionth gram of 1,4-dioxane per 1 liter of water [or ppb]). However, contaminated wells that may have been used as a source of drinking water have been reported to contain 1 mg per liter (1 ppm). 1,4-Dioxane has been detected in food vapors, which suggests that 1,4-dioxane may be a natural ingredient in some foods. Vapors from chicken, meat, tomato, and small shrimp have been reported to contain 1,4-dioxane. However, the amounts of 1,4-dioxane in other foods are not known.

Tap water can contain 1,4-dioxane, so you also can be exposed to 1,4-dioxane during activities such showering, bathing, and laundering. Exposure to 1,4-dioxane in tap water by breathing in

during showering or other indoor activities can result in higher exposures to 1,4-dioxane than from drinking water.

Your skin may contact 1,4-dioxane when you use cosmetics, detergents, and shampoos containing 1,4-dioxane. In 1985, the Food and Drug Administration (FDA) requested that manufacturers limit the level of 1,4-dioxane in cosmetic products to levels not greater than 10 milligrams of 1,4-dioxane per kilogram of product (10 mg/kg or 10 ppm). However, during 1992–1997, the average concentration of 1,4-dioxane in some cosmetic products reportedly ranged from 14 to 79 mg/kg. For more information, see Chapter 6.

1.4 HOW CAN 1,4-DIOXANE ENTER AND LEAVE MY BODY?

1,4-Dioxane can enter the body by contact of the skin with products that contain it or with contaminated soil, by breathing vapors that escape from liquids that contain 1,4-dioxane (as may happen when showering with contaminated water), or by eating contaminated food. Studies in volunteers have shown that after inhalation of vapors of 1,4-dioxane, almost all of the 1,4-dioxane that enters the lungs can pass to the blood stream. Studies in animals have shown that the same can occur with 1,4-dioxane that is swallowed and reaches the stomach. Much smaller amounts of 1,4-dioxane can pass to the bloodstream if it contacts your skin. Once in the bloodstream, 1,4-dioxane is distributed throughout the body and is rapidly converted into other chemicals, or metabolites, which quickly leave the body in the urine. Neither 1,4-dioxane nor its metabolites build up in the body. See Chapter 3 for more information about how 1,4-dioxane enters and leaves the body.

1.5 HOW CAN 1,4-DIOXANE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways to treat people who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing can help identify health problems, such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal-care guidelines because laws today protect the welfare of research animals.

Few studies are available that provide information about the effects of 1,4-dioxane in humans. Acute accidental exposure to high amounts of vapors of 1,4-dioxane that have caused death in people have been reported. In these cases, skin contact with the chemical also probably occurred. Autopsies of these patients showed extensive damage to the liver and kidneys. Volunteers who breathed controlled low levels of 1,4-dioxane vapors for short periods (minutes to hours) complained of irritation of the eyes and the nose. A few studies of workers exposed to 1,4-dioxane for long periods did not show any significant harmful health effects. Studies in animals have shown that breathing vapors of 1,4-dioxane, swallowing liquid 1,4-dioxane or contaminated drinking water, or having skin contact with liquid 1,4-dioxane also affects mainly the liver and kidneys. Animals that breathed high amounts of 1,4-dioxane also became drowsy. Scientists do not know whether 1,4-dioxane affects reproduction or the ability to fight infections in people or animals. The limited number of studies of workers did not indicate whether 1,4-dioxane causes cancer in humans. However, laboratory rats and mice that drank water containing 1,4-dioxane during most of their lives developed liver cancer; the rats also developed cancer inside the nose. Scientists are debating the degree to which the findings in rats and mice apply to exposure situations commonly encountered by people. On the basis of inadequate evidence in humans and sufficient evidence in experimental animals, the International Agency for Research on Cancer has determined that 1,4-dioxane is possibly carcinogenic to humans. The U.S. Department of Health and Human Services considers 1,4-dioxane as reasonably anticipated to be a human carcinogen on the basis of sufficient evidence of carcinogenicity in experimental animals. EPA has established that 1,4-dioxane is a probable human carcinogen on the basis of inadequate evidence in people and sufficient evidence in animals. It should be pointed out that the limited environmental monitoring data available suggest that the levels of

1,4-dioxane to which the general population might be exposed through contact or use of consumer products (including food), or that are normally found in environmental media, are generally significantly lower than those used in studies with experimental animals. See Chapter 3 for more information about how 1,4-dioxane can affect your health.

1.6 HOW CAN 1,4-DIOXANE AFFECT CHILDREN?

This section discusses potential health problems in people from exposures during conception to maturity (18 years of age).

Children can be exposed to 1,4-dioxane from contaminated air and food, and from drinking contaminated well or tap water; from showering or bathing with contaminated water; and from using consumer products that contain small amounts of 1,4-dioxane; however, based on available measurements, these risks are very low. It should be noted that exposure to 1,4-dioxane by breathing in evaporated contaminated water during showering or other indoor activities can result in higher exposures to 1,4-dioxane compared to drinking the tap water.

Children play outdoors and can be exposed if they touch or eat contaminated soil or place dirty objects in their mouths.

There are no studies of children exposed to 1,4-dioxane. However, children might experience health problems similar to those in adults if they were exposed to high concentrations of 1,4-dioxane. 1,4-Dioxane could harm children's liver and kidneys, depending on the amount of 1,4-dioxane entering the body.

Scientists do not know whether exposure of pregnant women to 1,4-dioxane can harm the unborn child, or if so, what levels of maternal exposure might harm the fetus. Not enough animal studies are available that can help predict what might happen in people. 1,4-Dioxane does not build up in the body, but a nursing mother exposed to a high amount of 1,4-dioxane might pass it to the infant in breast milk. However, scientists do not know whether this occurs in people or

animals. More information regarding children's health and 1,4-dioxane can be found in Section 3.7.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 1,4-DIOXANE?

If your doctor finds that you (or a family member) have been exposed to substantial amounts of 1,4-dioxane, ask whether your children also might have been exposed. Your doctor might need to ask your state health department to investigate.

Families that drink water that could be contaminated with 1,4-dioxane can reduce the risk for exposure to 1,4-dioxane by drinking uncontaminated bottled water. Children who live near hazardous waste sites that might be contaminated with 1,4-dioxane should be discouraged from playing in mud and water near these sites because these sites might contain 1,4-dioxane. Children also should be discouraged from eating mud, and they should follow careful hand washing.

1,4-Dioxane may be a contaminant in cosmetics, detergents, and shampoos that contain the following ingredients (which may be listed on the product label): "PEG," "polyethylene," "polyethylene glycol," "polyoxyethylene," "-eth-," or "-oxynol-." Most manufacturers remove 1,4-dioxane from these ingredients to concentrations recommended by the FDA as safe. Thus, most products on the market today contain 1,4-dioxane in very small amounts or not at all. However, some cosmetics, detergents, and shampoos may contain 1,4-dioxane at levels higher than recommended by FDA. Because products contaminated at concentrations higher than the FDA-recommended levels are not possible to determine without testing, families should avoid using products containing the ingredients listed above unless the manufacturer can guarantee that 1,4-dioxane is below the FDA-recommended level.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,4-DIOXANE?

1,4-Dioxane and its breakdown products can be measured in your blood and urine, and positive results indicate you have been exposed to 1,4-dioxane. The tests are not routinely available at your doctor's office because they require special equipment, but the doctor can collect the samples and send them to a special laboratory. The tests need to be conducted within days after the exposure because 1,4-dioxane and its breakdown products leave the body fairly rapidly. These tests do not predict whether exposure to 1,4-dioxane will produce harmful health effects. For more information, see Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. EPA, the Occupational Safety and Health Administration (OSHA), and FDA are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) are two federal agencies that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels—in other words, levels of a toxic substance in air, water, soil, or food that do not exceed critical levels that are usually based on levels that affect animals; they are then adjusted to levels that will help protect people. Sometimes these not-to-exceed levels differ among federal agencies because the agencies used different exposure times (for example, an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are updated periodically as more information becomes available. For the most current information, check with the federal agency that provides it.

EPA recommends that the levels of 1,4-dioxane in drinking water that children drink for 1 day not exceed 4 milligrams per liter (mg/L) or 0.4 mg/L if they drink the water for 10 days. However, a federal drinking water standard (maximum contaminant level or MCL) is not available. EPA requires that any release to the environment of 100 pounds of 1,4-dioxane or more be reported EPA.

OSHA has established a workplace exposure limit for 1,4-dioxane of 360 mg/m^3 (100 ppm), for an 8-hour workday, 40 hours per week. NIOSH recommends that workers not be exposed to more than 3.6 mg/m^3 (1 ppm) of 1,4-dioxane in the air over 30 minutes. NIOSH also recommends that a level of 1,800 mg/m^3 (500 ppm) of 1,4-dioxane in the air be considered as immediately dangerous to life and health.

FDA keeps a record of raw materials and products contaminated with 1,4-dioxane. For more regulations and guidelines applicable to 1,4-dioxane, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and

technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mailing atsdric@cdc.gov, or by writing to

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

For-profit organizations may request copies of final Toxicological Profiles from

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,4-DIOXANE IN THE UNITED STATES

1,4-Dioxane is a stable, clear liquid at ambient temperatures and is miscible with water. It is used primarily as a solvent for chemical processing (e.g., adhesives, cleaning and detergent preparations, cosmetics, deodorant fumigants, emulsions and polishing compositions, fat, lacquers, pulping of wood, varnishes, waxes). It has also been used as a laboratory reagent; in plastic, rubber, insecticides, and herbicides; as a chemical intermediate; as part of a polymerization catalyst; and as an extraction medium of animal and vegetable oils. 1,4-Dioxane may also be found as a contaminant in ethoxylated surfactants, which are used in consumer cosmetics, detergents, and shampoos. Currently, manufacturers remove 1,4-dioxane from ethoxylated surfactants to low levels by vacuum stripping.

Human exposure to 1,4-dioxane may occur by inhalation, ingestion, and dermal contact. Because 1,4-dioxane may be found in tap water, human exposure to 1,4-dioxane may also occur during activities such as showering, bathing, and laundering. Exposure to 1,4-dioxane in tap water through inhalation during showering or other indoor activities can result in higher exposures to 1,4-dioxane compared to ingestion of drinking water.

Current levels of 1,4-dioxane in ambient air, drinking water, and food samples are not available. In the mid 1980s, levels 1,4-dioxane in ambient outdoor air ranged from 0.1 to 0.4 $\mu g/m^3$ (0.028–0.11 ppb). Mean concentrations of 1,4-dioxane in indoor air were a factor of 10 higher at 3.704 $\mu g/m^3$ (1.029 ppb). In the 1970s, municipal water supplies in the United States were reported to contain 1 µg/L (ppb) of 1,4-dioxane. 1,4-Dioxane has been detected in food volatiles which may indicate that 1,4-dioxane may be a natural constituent in some foods. Volatiles from chicken, meat, tomatoes, and small shrimp have been reported to contain 1,4-dioxane at unquantified levels. Dermal exposure to 1,4-dioxane may occur with the use of consumer cosmetics, detergents, and shampoos containing ethoxylated surfactants. In 1985, the FDA instituted a formal policy that cosmetic products should not contain 1,4-dioxane at concentrations >10 ppm (mg/kg). However, in products (e.g., children's shampoos and bubble baths) analyzed since 1994, the FDA observed that the downward trend in the levels of 1,4-dioxane previously observed in the late 1980s was no longer evident in the products analyzed in the 1990s. Between the years 1992 and 1997, the average concentration of 1,4-dioxane in cosmetic finished products was to reported fluctuate from 14 to 79 ppm (mg/kg).

2.2 SUMMARY OF HEALTH EFFECTS

Limited information exists regarding the health effects of 1,4-dioxane in humans. Yet, the available data is sufficient to clearly identify the liver and kidneys as the target organs for 1,4-dioxane toxicity following short-term exposure to relatively high amounts of 1,4-dioxane, regardless of the route of exposure. This has been corroborated in studies in animals. Workplace exposures to undetermined, but presumably high concentrations of 1,4-dioxane have resulted in death. Inhalation was the most likely route of exposure, although considerable dermal contact may also have taken place. Evaluation of the subjects prior to death did not provide a picture that could be considered unique to 1,4-dioxane. Subjects often complained of gastrointestinal pain, had high blood pressure, anuria, leukocytosis, and exhibited signs of nervous system involvement. The deaths occurred 5–8 days after the initial symptoms of illness. Postmortem evaluation revealed extensive liver and kidneys damage and in three out of five cases described in one study. kidney disease was considered to be the direct cause of death. Controlled exposures of volunteers for periods ranging from a few minutes to 6 hours produced eye, nose, and throat irritation. The lowest exposure concentration that produced eye irritation was 50 ppm during a 6-hour exposure, but exposure in a much older study to 2,000 ppm for 3 minutes produced no complaints of eye or nasal discomfort. Little is known about long-term exposure to lower concentrations of 1,4-dioxane. A study of German workers exposed to 0.006–14.3 ppm 1,4-dioxane for an average of 25 years found no evidence of liver or kidney disease or any other clinical effects. An additional study that examined mortality rates among workers employed at a manufacturing and processing facility in the United States found no differences between observed and expected incidences of cancer. However, this study was limited in size and exposure duration. No information was available regarding reproductive, developmental, or immunological effects of 1,4-dioxane in humans.

As previously mentioned, the liver and kidneys are also targets of 1,4-dioxane toxicity in animals and this has been described following inhalation, oral, and dermal exposure. There are no studies of the effects of 1,4-dioxane on reproductive function or immunocompetence in animals, and only one study in rats evaluated developmental end points following oral exposure during gestation. Slight fetotoxicity occurred at a dose level that also affected the mothers. Chronic administration of 1,4-dioxane in the drinking water produced liver cancer in rats, mice, and guinea pigs, and cancer of the nasal cavity in rats. However, a 2-year inhalation study in rats exposed to relatively low concentrations of 1,4-dioxane (111 ppm) provided no evidence of carcinogenicity or any other health effect. The mechanism of carcinogenicity of 1,4-dioxane has not been elucidated, but the lack of or weak genotoxicity of

1,4-dioxane, its strong promotion properties, and the extensive cytotoxicity observed in some studies at dose levels that induce tumors suggest that 1,4-dioxane may be acting through a non-genetic mode of action, and has led some to suggest that perhaps the carcinogenic potency of 1,4-dioxane should be reassessed. Indeed, the EPA is currently re-evaluating the health assessment for 1,4-dioxane.

Only cancer (with emphasis on the liver) and kidney effects are discussed below since these are the effects of most concern should humans be accidentally acutely exposed to 1,4-dioxane or populations be identified that are being exposed to low-level, long-term exposure to this chemical.

Liver and Cancer Effects. Liver effects have occurred in humans and animals exposed to 1,4-dioxane, and the data in animals suggest that they occur regardless of the route of exposure. An occupational study and a case report provided a detailed description of the liver pathology in subjects following exposure to 1,4-dioxane that resulted in deaths within 1–2 weeks after the increased exposure. In the occupational study, five lethal cases were described; upon postmortem examination, enlarged and pale liver and centrilobular necrosis were commonly observed. None of the subjects showed jaundice before death. Similar observations were made in the lethal case report. Neither workers exposed to lower concentrations of 1,4-dioxane for many years nor volunteers exposed for a single 6-hour period to 50 ppm 1,4-dioxane (Young et al. 1977) showed indications of liver alterations.

One study provided detailed descriptions of liver pathology in several animal species exposed intermittently to 1,4-dioxane by inhalation for period of up to 13 weeks and also exposed orally and by dermal contact. Both lethal and non-lethal concentrations (1,000–10,000 ppm) caused degrees of degeneration that varied from cloudy swelling to large areas of complete necrosis. Similar effects were seen following oral and dermal exposure. Hepatocyte vacuolation and swelling were reported in mice and rats dosed with 1,4-dioxane in the drinking water for 2 or 13 weeks. Evidence of hepatic degenerative changes was seen in Sherman rats that died after 2–4 months of treatment in a 2-year drinking water bioassay. Long-term oral studies in animals described hepatocellular degeneration and necrosis in Sherman rats at about 94 mg 1,4-dioxane/kg/day and liver hyperplasia in Fischer 344 rats at about 81 mg/kg/day; hepatocytomegaly was observed in female Osborne-Mendel rats treated with approximately 350 mg/kg/day. The apparent different lesions and thresholds for the effects in the liver may reflect strain differences.

All long-term studies in rats dosed with 1,4-dioxane via the drinking water reported an increased incidence of liver tumors. In the better reported studies, tumor development occurred at doses that

produced hepatocellular hyperplasia and degeneration and evidence of hepatic regeneration. 1,4-Dioxane also induced tumors in the nasal turbinates in rats and liver tumors in mice. The mechanism of carcinogenicity of 1,4-dioxane has not been elucidated, but the results from several lines of investigation have led some to conclude that 1,4-dioxane has a non-genotoxic, yet unknown, mode of action.

The EPA has developed cancer risk values for 1,4-dioxane based on the increased incidence of tumors of the nasal cavity in male Osborne-Mendel rats in a 2-year drinking-water bioassay. The relevance of these tumors to humans has been questioned. It was suggested that the tumors resulted from inspiration of water containing 1,4-dioxane into the nasal cavity. Preliminary studies with a dye in the drinking water have demonstrated that large amounts of inhaled water may be deposited directly in the nose. The lack of nasal tumors in mice in chronic oral studies could be due to different tissue sensitivity and/or repair mechanism, or to a difference in anatomical features. Also, the lack of nasal cytotoxicity and nasal tumors in Wistar rats exposed intermittently to 111 ppm 1,4-dioxane in the air for 2 years suggests that the minimal effective dose may not have been reached.

Liver toxicity has been proposed to be necessary for liver tumor formation possibly in rats but not in mice. Since this suggests to some scientists the existence of a threshold, they have suggested using approaches other than the Linearized Multistage Model for estimating human cancer risk due to exposure to 1,4-dioxane. In addition, the use of available physiologically based pharmacokinetic (PBPK) models may provide a means for estimating the internal dose of 1,4-dioxane or metabolites delivered to the target organ from the doses administered in the animal bioassays and extrapolating. Based on inadequate evidence in humans and sufficient evidence in experimental animals, the International Agency for Research on Cancer (IARC) has determined that 1,4-dioxane is possibly carcinogenic to humans. The Department of Health and Human Services (DHHS) has stated that 1,4-dioxane is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. The EPA has established that 1,4-dioxane is a probable human carcinogen based on inadequate evidence in humans and sufficient evidence in animals. The EPA is currently re-evaluating the health assessment for 1,4-dioxane.

Renal Effects. Kidney lesions appeared to be the cause of death of five workers who were exposed to unknown concentrations of 1,4-dioxane primarily by the inhalation route. Death occurred 1–2 weeks after episodes of elevated exposure started at work. All five cases experienced oliguria or anuria. Post mortem examination revealed swollen kidneys with hemorrhages and necrosis of the cortex. Similar findings were reported in a fatal case report. No renal alterations, as judged by urinalyses, were described

in other reports of long-term occupational exposure to low levels of 1,4-dioxane or in a group of volunteers following a single 6-hour exposure to 50 ppm 1,4-dioxane. Very similar kidney lesions were observed in animals exposed to 1,4-dioxane by several routes of exposure. Rodents exposed to acutely lethal concentrations of 1,4-dioxane showed severe kidney damage consisting in marked patchy cell degeneration of the cortical tubules and intense vascular congestion and hemorrhages both inter- and intra-tubular. Well-marked kidney lesions were present in animals that survived intermittent inhalation exposure for up to 12 weeks. Similar observations were made in intermediate-duration studies in rats and mice exposed orally and in guinea pigs and rabbits following dermal application of 1,4-dioxane. Evidence of renal degenerative changes was seen in Sherman rats that died after 2–4 months of treatment in a 2-year drinking water bioassay. Nuclear enlargement of the proximal tubule was reported in rats in a 13-week study. Increased incidence of degeneration and necrosis of the tubular epithelium was seen in rats that survived until termination of the study and similar findings were reported in Osborne-Mendel rats. Hematuria and nuclear enlargement of the proximal tubule were reported in Fischer-344 rats, and hematuria, proteinuria, and glucosuria were noted in Crj:BDF_1 mice in a 2-year drinking water study. No compound-related neoplastic lesions were observed in the kidneys in other long-term studies conducted with 1,4-dioxane in rodents. The mechanism(s) by which 1,4-dioxane induces kidneys lesions is not known, and virtually no discussion about this topic was found in the reviews available. The findings in the cases studies are consistent with an acute nephritic syndrome, which is characterized by acute renal failure and oliguria. It is not expected that exposure to concentrations commonly in the environment would cause adverse kidney effects in humans.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 2 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 1,4-dioxane.

The acute-duration inhalation MRL is based on a minimal lowest-observed-adverse-effect level (LOAEL) of 50 ppm for eye irritation in humans (Young et al. 1977). In that study, the effects of 50 ppm 1,4-dioxane vapors were evaluated in four healthy male volunteers. Prior to the study, the subjects provided a complete history and underwent tests including chest x-ray, EKG, respiratory function tests, a conventional battery of 12 blood chemistry tests plus triglyceride and creatinine determinations, and complete hematological and urine analyses. Except for the chest x-ray, the tests were repeated 24 hours

and 2 weeks after the exposure. The exposure was carried out in a 26.7 m^3 chamber under dynamic airflow conditions. The tests conducted 24 hours and 2 weeks after exposure did not reveal any exposure-related abnormalities, but no data were provided in the study. Eye irritation was a frequent and the only complaint throughout the exposure. Tolerance to the odor of 1,4-dioxane occurred during exposure. Two of the subjects could not perceive the odor after 4 and 5 hours in the chamber. The LOAEL of 50 ppm was divided by an uncertainty factor of 30 (3 for a minimal LOAEL and 10 to protect sensitive populations). Because the effects observed were local irritation effects, they were not time-dependent, and an adjustment to 24-hour exposure was not necessary.

Other studies with volunteers support the finding of Young et al. (1977). For example, Silverman et al. (1946) exposed 12 subjects to various concentrations of 1,4-dioxane for only 15 minutes and determined a no-observed-adverse-effect level (NOAEL) of 200 ppm for eye and nose irritation; the LOAEL was 300 ppm. Wirth and Klimmer (1936) reported that slight mucous membrane irritation started to take place in volunteers exposed to concentrations about 278 ppm for a few minutes (unspecified) and that at 1,390 ppm for several minutes, the subjects described prickling in the nose and scratchiness and dryness in the throat. Fairley et al. (1934) reported a NOAEL of 2,000 ppm (only level tested) for respiratory and ocular effects in six subjects exposed to 1,4-dioxane for only 3 minutes. Finally, Yant et al. (1930) described slight eye, nose, and throat irritation in a group of five subjects exposed to 1,600 ppm (only level tested) 1,4-dioxane for only 10 minutes. The available studies in animals used exposure concentrations much higher than the one tested by Young et al. (1977) that often caused death among the animals.

Because there were no adequate intermediate-duration inhalation studies in humans or animals from which to derive an intermediate-duration inhalation MRL, the chronic-duration inhalation MRL of 1 ppm (see derivation below) was adopted also for intermediate-duration exposure. The intermediate-duration database for 1,4-dioxane consists of one early study that reports the effects of 1,4-dioxane in several animal species exposed to high doses (lethal in some cases) of 1,4-dioxane (Fairley et al. 1934). Rats, mice, guinea pigs, and rabbits were exposed 3 hours/day, 5 days/week for periods of up to 12 weeks. At termination, examination of the animals revealed moderate to severe liver and kidney toxicity occurring at all exposure levels in all of the species tested. The lowest exposure level was 1,000 ppm.

- An MRL of 1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to 1,4-dioxane.

The MRL is based on a NOAEL of 111 ppm for liver effects in Wistar rats (Torkelson et al. 1974) and application of the physiologically-based pharmacokinetic (PBPK) model of Reitz et al. (1990). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were provided by Dr. Richard Reitz. A detailed description of the model and its application is presented in Appendix B. In the Torkelson et al. (1974) study, groups of Wistar rats (288/sex) were exposed to 1,4-dioxane vapors at a concentration of 0.4 mg/L (111 ppm) 7 hours/day, 5 days/week for 2 years. Controls were exposed to filtered room air. End points examined included clinical signs, eye and nasal irritation, skin condition, respiratory distress, and tumor formation. Hematological parameters (hemoglobin, red blood cell count, total and differential leukocyte counts, corpuscular volume) were determined after 16 and 23 months of exposure. Blood collected at termination was used also for determination of clinical chemistry parameters (serum alanine aminotransferase [ALT] and alkaline phosphatase activity, BUN, total protein). Liver, kidneys, and spleen were weighed and the major tissues and organs were processed for microscopic examination. Exposure to 1,4-dioxane vapors had no significant effect on mortality, or body weight gain and induced no signs of eye or nasal irritation or respiratory distress. Slight but statistically significant changes in hematological and clinical chemistry parameters were within the normal physiological limits and were considered of no toxicological importance. Organ weights were not significantly affected. Microscopic examination of organs and tissues did not reveal treatment-related effects. Because the only exposure level tested did not cause any significant adverse effects, the true study NOAEL is likely to be higher than 111 ppm. Using the Reitz et al. (1990) model for interspecies extrapolation of 1,4-dioxane dosimetry for data from the Torkelson et al. (1974) study yields a human equivalent NOAEL of 35.5 ppm. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) yields a chronic-duration inhalation MRL of 1 ppm. Using EPA's standard methodology for extrarespiratory effects for a category 3 gas rather than the PBPK model, and an uncertainty factor of 30, results in an MRL of 2 ppm for 1,4-dioxane. The derivation using the PBPK model is preferred because it yields a more protective MRL.

The limited human data supports the chronic-duration inhalation MRL. An occupational study by Thiess et al. (1976) provided no evidence of ill effects in a group of 74 German workers exposed to concentrations ranging from 0.006 to 14.3 ppm for an average of 25 years. In another epidemiological study, mortality rates were evaluated among workers exposed to 0.1–17 ppm 1,4-dioxane for up to 21 years (Buffler et al. 1978). No differences were found between observed and expected incidences of cancer.

Oral MRLs

- An MRL of 4 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to 1,4-dioxane.

The acute-duration oral MRL is based on a NOAEL of 370 mg/kg/day for nasal effects in a study in rats (JBRC 1998a). In that study, F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 1,110, 3,330, 10,000, 30,000, or 90,000 ppm for 2 weeks (0, 130, 370, 1,010, or 2,960 mg/kg/day for males; 0, 160, 400, 1,040, or 2,750 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body weight, gross necropsy, and histopathology on 2–3 animals per group. All animals in the 90,000 ppm group died. Two females in the 30,000 ppm (2,750 mg/kg/day) died. Body weight gain was reduced by about 25% in males and females from the 30,000 ppm groups (2,960 mg/kg/day for males, 2,750 mg/kg/day for females). Food and water consumption was reduced approximately by 30% in males and females from the 30,000 ppm group. At 30,000 ppm (2,960 mg/kg/day for males; 2,750 mg/kg/day for females), there was nuclear enlargement of the olfactory epithelium, swelling and vacuolar changes of the central area in the liver, hydropic change of the proximal renal tubule, and vacuolar changes in the brain. At 10,000 ppm, there was nuclear enlargement of the olfactory epithelium (1,010 mg/kg/day in males; 1,040 mg/kg/day in females). The study NOAEL was 400 mg/kg/day in females and 370 mg/kg/day in males (3,330 ppm). Therefore, the dose level of 370 mg/kg/day in male rats is used as basis for the MRL. The MRL of 4 mg/kg/day was calculated by dividing the male NOAEL of 370 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations). It should be pointed out that the study has several limitations, including the lack of statistical analysis of the results, only a small number (2–3) of animals were examined, and end points such as hematology, clinical chemistry, clinical signs, and gross examinations were not conducted or reported. Although these limitations compromise the study, the findings are consistent with what is known about target organs for 1,4-dioxane. JBRC (1998a) conducted a similar study in male and female Crj:BDF_1 mice and identified NOAELs of 1,380 and 1,780 mg/kg/day for liver effects in males and females, respectively. Doses of 2,550 and 3,220 mg/kg/day caused swelling of the central area of the liver in males and females, respectively. No nasal effects were observed in the mice.

Most of the rest of the acute database consists of high-dose early studies aimed at determining LD_{50} values (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Pozzani et al. 1959; Smyth et al. 1941). The lowest dose that caused lethality was 327 mg 1,4-dioxane/kg/day in a study that tested only three dogs (Schrenk and Yant 1936). This dose was provided in the drinking water and killed one dog

after 10 days of treatment. Doses of 375 mg/kg/day killed another dog in 9 days. However, because the dogs were allowed to drink the 1,4-dioxane solution only twice daily and no other source of water was available, dehydration may have played a role in the death of the animals. A gestational exposure study in rats identified a maternal and developmental NOAEL and LOAEL of 513 and 1,033 mg/kg/day, respectively (Giavini et al. 1985).

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,4-dioxane.

The intermediate-duration oral MRL is based on a NOAEL of 60 mg 1,4-dioxane/kg/day for liver effects in rats (JBRC 1998b). In that study, groups of F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 640, 1,600, 4,000, 10,000, or 25,000 ppm for 13 weeks (0, 60, 150, 330, 760, or 1,900 mg/kg/day in males; 0, 100, 200, 430, 870, or 2,020 mg/kg/day in females). End points evaluated included clinical signs, food and water consumption, body weight, complete hematology and clinical chemistry tests, urinalysis, organ weights, gross necropsy, and histopathology. One female in the 25,000 ppm (2,020 mg/kg/day) died. Body weight gain was reduced at 870 mg/kg/day (12%) and 2,020 mg/kg/day (21%) in females and 1,900 mg/kg/day (21%) in males. Food consumption was reduced 13% in females at 2,020 mg/kg/day. Water consumption was reduced in a dose-related manner in all male groups and in females at ≥200 mg/kg/day. Hematology tests showed significant increases in erythrocyte counts, hemoglobin, hematocrit, and neutrophils, and a decrease in lymphocytes in males at 1,900 mg/kg/day, and decreases in mean corpuscular volume and platelets in females at 2,020 mg/kg/day. Total protein and albumin were decreased in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Serum aspartate aminotransferase (AST), ALT, alkaline phosphatase (AP), and leucine aminopeptidase (LAP) activities, and levels of cholesterol, triglycerides, sodium, and glucose were significantly elevated in high dose males and females. Urinary pH was decreased in males at ≥330 mg/kg/day and in females at ≥870 mg/kg/day. Absolute and relative kidney weights were increased in females at ≥200 mg/kg/day. Nuclear enlargement of the respiratory epithelium occurred in males at ≥150 mg/kg/day and in females at ≥200 mg/kg/day; nuclear enlargement of the olfactory and tracheal epithelium occurred in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Swelling of the central area of the liver was observed in males at ≥150 mg/kg/day and in females at ≥870 mg/kg/day, and vacuolar changes in the liver occurred in males at ≥760 mg/kg/day and in females at 2,020 mg/kg/day. Nuclear enlargement of the proximal tubule of the kidneys was seen in males at ≥760 mg/kg/day and in females at ≥870 mg/kg/day. Hydropic changes in the proximal tubule of the kidneys and vacuolar changes in the brain occurred in high-dose males and females (1,900 and 2,020 mg/kg/day, respectively). The study LOAEL was 150 mg/kg/day for liver and nasal effects in male rats. Limitations of the study

include the lack of reporting on clinical signs and gross necropsy. To derive the MRL, the NOAEL of 60 mg/kg/day for liver effects in males was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations), yielding an intermediate-duration oral MRL of 0.6 mg/kg/day.

A study by Lundberg et al. (1987) supports the liver findings of JBRC (1998b). The study used male Sprague-Dawley rats (8–11/group) that were treated with 100 or 1,000 mg 1,4-dioxane/kg by gavage in saline 5 days/week for 7 weeks. One week after the last treatment, the rats were killed and the livers were processed for microscopic examination. The livers of high-dose rats showed enlarged foamy hepatocytes mainly in midzonal regions. The foamy appearance was due to vacuoles shown to contain fat. No treatment-related histopathological alterations were observed in the liver at the 100 mg/kg/day dose level.

- An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,4-dioxane.

The chronic-duration oral MRL is based on a NOAEL of 9.6 mg 1,4-dioxane/kg/day for liver effects in male rats in a study by Kociba et al. (1974). In that study, groups of Sherman rats (60/sex/dose level) were treated with 1,4-dioxane in the drinking water at levels of 0 (controls), 0.01, 0.1, or 1% for 716 days. Based on body weight and water consumption data, the investigators estimated that the water provided doses of 1,4-dioxane of 0, 9.6, 94, and 1,015 mg/kg/day for males and 0, 19, 148, and 1,599 mg/kg/day for females. Blood samples were collected from controls and high-dose rats during the 4th, 6th, 12th, and 18th months of the study and at termination. Additional end points evaluated included clinical signs, body weight, organ weights, and gross and microscopic examination of major tissues and organs. Treatment with 1,4-dioxane significantly increased mortality in high-dose males and females beginning at about 2–4 months of treatment. These rats showed degenerative changes in both the liver and kidneys. Water consumption was significantly reduced in high-dose animals during the first year of the study. Body weight gain was significantly reduced in high-dose animals from the beginning of the study. Microscopic lesions were restricted to the liver and kidneys from the mid- and high-dose groups. The liver lesions consisted of various degrees of hepatocellular degeneration and necrosis and evidence of hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation. The NOAEL for liver effects was 9.6 mg/kg/day in males and 19 mg/kg/day in females. The LOAELs were 94 mg/kg/day in males and 148 mg/kg/day in females. The kidneys showed tubular epithelial degeneration and necrosis, and there was evidence of renal tubular regeneration as indicated by increased tubular epithelial regenerative activity. There were no compound-related alterations in hematological parameters at any time point. The MRL of 0.1 mg/kg/day was calculated by dividing the male rat NOAEL of

9.6 mg/kg/day by an uncertainty factor of 100 (10 to protect sensitive populations and 10 for animal to human extrapolation). The carcinogenic effects were limited to the liver and nasal turbinates from high-dose animals.

The NOAEL and LOAEL for liver effects from Kociba et al. (1974) are supported by the results of JBRC (1998c). In that study, groups of Fischer 344/DuCrj rats (50/sex/dose level) received 1,4-dioxane in the drinking water for 104 weeks. 1,4-Dioxane was administered at levels of 0, 200, 1,000, and 5,000 ppm for 2 years (0, 16, 81, and 398 mg/kg/day for males; 0, 21, 103, and 514 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body and organ weights, comprehensive hematology and clinical chemistry tests, urinalysis, and gross and microscopic examination of major organs and tissues. In males, relative liver weight was increased at ≥81 mg/kg/day and absolute liver weight was increased at 398 mg/kg/day. A significant increase incidence of spongiosis, hyperplasia, and clear and mixed cell foci was observed in the liver from male rats with ≥81 mg 1,4-dioxane/kg/day, but not 16 mg/kg/day. These lesions were observed in females dosed with 514 mg/kg/day, but not with lower doses. In addition, in this study, female rats dosed with ≥103 mg 1,4-dioxane/kg/day showed nuclear enlargement of the olfactory epithelium of the nasal cavity; no such lesions occurred with the lower female rat dose of 21 mg/kg/day.

The NCI (1978) bioassay in Osborne-Mendel rats used somewhat higher dose levels than Kociba et al. (1974) and JBRC (1998c), but did not observe liver lesions in male rats dosed with 240 mg 1,4-dioxane/kg/day, a dose level that caused liver hyperplasia in male Fischer 344 rats dosed with 81 mg/kg/day or that caused hepatocyte degeneration in Sherman rats dosed with 94 mg/kg/day. Since the dosing method was the same in the three studies, the drinking water, the different results may reflect differences in strain sensitivity.

An alternate approach to derive a chronic-duration oral MRL is to use the PBPK model developed by Reitz et al. (1990), as was done above for the chronic inhalation data. Using the model, it can be estimated that the human equivalent dose to the NOAEL of 9.6 mg/kg/day for liver effects in males is 12.9 mg/kg/day. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) to the human NOAEL of 12.9 mg/kg/day yields a chronic-duration oral MRL of 0.4 mg/kg/day, which supports the MRL of 0.1 mg/kg/day derived above. A detailed explanation of the use of the model is presented in Appendix B.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,4-dioxane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,4-dioxane are indicated in Table 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,4-dioxane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Several cases of death in humans have been documented after exposure to high concentrations of 1,4-dioxane. Barber (1934) described five deaths that occurred within a period of 2 weeks among factory workers engaged in a process that involved primarily exposure to 1,4-dioxane vapors, although minimal dermal exposure could have not been avoided. Three of the subjects suffered from abdominal pain and vomiting before death occurred. Post-mortem examination of the subjects showed extensive gross and microscopic lesions to the liver and kidneys. Based on his observations, Barber (1934) suggested that the effects on the kidneys may have been responsible for the fatal outcome and that liver necrosis, although widespread, was compatible with recovery. No exposure levels were available in these case reports. Johnstone (1959) described an additional fatal case of a worker exposed to 1,4-dioxane for only 1 week and whose post-mortem examination showed kidney and liver alterations similar to those described by Barber (1934). In the Johnstone case, the room in which the patient had worked had no exhaust ventilation and the worker was not provided a respirator. The minimum concentration of 1,4-dioxane in the room was 208 ppm and the maximum was in excess of 650 ppm; the average concentration was 470 ppm. In addition, dermal exposure may have been considerable in this case.

Studies in animals, mostly early studies, provide information on lethality of relatively high concentrations of 1,4-dioxane in several species and also indicate that the kidneys and liver, and in some cases, the lungs, are the main targets of high airborne concentrations of 1,4-dioxane. Short-term exposure to 5,000 ppm 1,4-dioxane was lethal to rats, mice, and rabbits, whereas 10,000 ppm was lethal to guinea pigs (Fairley et al. 1934). A 4-hour LC_{50} of 14,261 ppm was calculated for rats (Pozzani et al. 1959). An additional study in guinea pigs reported that the minimum period of exposure that caused the death of the majority of a group of six animals was 180 minutes to 30,000 ppm; no deaths occurred in groups exposed to up to 10,000 ppm for up to 480 minutes (Yant et al. 1930). One out of four rabbits exposed to 2,000 ppm 1,4-dioxane 3 hours/day, 5 days/week died on week 4 of exposure, and the cause of death was attributed to renal and hepatic lesions (Fairley et al. 1934).

The LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals following inhalation exposure to 1,4-dioxane. No studies were located regarding endocrine, dermal, or body weight effects in humans after inhalation exposure to 1,4-dioxane.

The highest NOAEL and all reliable LOAEL values from each study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. In a group of six individuals exposed to 2,000 ppm 1,4-dioxane vapors for 3 minutes in a 10 m^3 chamber, there were no complaints of nasal discomfort, but one out of four subjects exposed to 1,000 ppm for 5 minutes complained of constriction of the throat (Fairley et al. 1934); however, the exposure concentrations were not verified. Exposure of five subjects to about 278 ppm for a few minutes (unspecified) produced slight mucous membrane irritation, and 1,390 ppm caused a slight prickling in the nose, and scratchiness and dryness in the throat (Wirth and Klimmer 1936). Exposure to 300 ppm 1,4-dioxane for 15 minutes produced nose and throat irritation among a group of 12 volunteers (Silverman et al. 1946). At 200 ppm, the report does not indicate the presence or absence of symptoms, but considers the exposure acceptable. A 10-minute exposure to 1,600 ppm 1,4-dioxane produced slight nose and throat irritation that persisted throughout the test in a group of five individuals (Yant et al. 1930). In another experiment by the same investigators, exposure of the same five persons to 5,500 ppm 1,4-dioxane for 1 minute resulted in a burning sensation to the nose and throat (Yant et al. 1930). Exposure of four men to 50 ppm for 6 hours reportedly caused no adverse respiratory signs or alterations in respiratory function, assessed 24 hours and 2 weeks after exposure (Young et al. 1977); however, no data were provided in the study.

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL: Less Serious (ppm)	LOAEL: Serious (ppm)		Reference Chemical Form
	ACUTE EXPOSURE							
	Death							
1	Rat (NS)	1 wk 5 d/wk 3 hr/d				5000	(3/3 deaths before a total of 16 hours of exposure)	Fairley et al. 1934
2	Rat (Wistar)	4 hr				14261 F	(4-hr LC50)	Pozzani et al. 1959
3	Mouse (NS)	1 wk 5 d/wk 3 hr/d				5000	(1/3 deaths after 3 hours of exposure)	Fairley et al. 1934
4	Gn Pig (NS)	1 wk 5 d/wk 3 hr/d				10000	(6/6 deaths before 7.5 hours of exposure)	Fairley et al. 1934
5	Gn Pig (NS)	10-540 min				30000	(death of majority of animals in 180 minutes)	Yant et al. 1930
6	Rabbit (NS)	1 wk 5 d/wk 3 hr/d				5000	(1/4 death after 16.5 hours of exposure)	Fairley et al. 1934

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
7	Human	5 min	Resp		1000 (1/4 throat constriction)		Fairley et al. 1934
8	Human	3 min	Resp	2000			Fairley et al. 1934
			Ocular	2000			
9	Human	15 min	Resp	200	300 (nose and throat irritation)		Silverman et al. 1946
			Ocular	200	300 (eye irritation)		
10	Human	10 min	Resp		1600 (slight nose and throat irritation)		Yant et al. 1930
			Ocular		1600 (slight eye irritation and lacrimation)		

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL: Less Serious (ppm)		LOAEL: Serious (ppm)		Reference Chemical Form
11	Human	6 hr	Resp	50 M					Young et al. 1977
			Cardio	50 M					
			Hemato	50 M					
			Hepatic	50 M					
			Renal	50 M					
			Ocular		50[b] M	(eye irritation)			
12	Rat (CD)	4 hr	Hepatic		1000 M	(increased serum transaminases indicative of liver injury)			Drew et al. 1978
13	Gn Pig (NS)	10-540 min	Resp		1000	(immediate nasal irritation)	30000	(dyspnea, gasping, shallow breathing, hyperemia, congestion)	Yant et al. 1930
			Ocular	1000	2000	(eye irritation)			

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Neurological						
14	Rat (Wistar)	2 wk 5 d/wk 4 hr/d		1500 F	3000 F (depressed avoidance response)		Goldberg et al. 1964
	INTERMEDIATE EXPOSURE						
	Death						
15	Rabbit (NS)	3-12 wk 5 d/wk 3 hr/d				2000 (1/4 death on week 4 of exposure)	Fairley et al. 1934
	Systemic						
16	Rat (NS)	3-12 wk 5 d/wk 3 hr/d	Resp	1000			Fairley et al. 1934
			Hepatic			1000 (hepatocyte degeneration)	
			Renal			1000 (renal cortex degeneration)	
17	Mouse (NS)	3-12 wk 5 d/wk 3 hr/d	Resp	1000			Fairley et al. 1934
			Hepatic			1000 (hepatocyte degeneration)	
			Renal			1000 (renal cortex degeneration)	

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
18	Gn Pig (NS)	3-12 wk 5 d/wk 3 hr/d	Resp	5000				Fairley et al. 1934
			Hepatic			1000	(hepatocyte degeneration)	
			Renal			1000	(cortical cell degeneration)	
19	Rabbit (NS)	3-12 wk 5 d/wk 3 hr/d	Resp	1000				Fairley et al. 1934
			Hepatic			1000	(hepatocyte degeneration)	
			Renal			1000	(cortical cell degeneration)	

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
20	Rat (Wistar)	2 yr 5 d/wk 7 hr/d	Resp	111			Torkelson et al. 1974
			Cardio	111			
			Gastro	111			
			Hemato	111			
			Hepatic	111[c]			
			Renal	111			
			Endocr	111			
			Dermal	111			
			Ocular	111			
			Bd Wt	111			
	Immuno/ Lymphoret						
21	Rat (Wistar)	2 yr 5 d/wk 7 hr/d		111			Torkelson et al. 1974
	Neurological						
22	Rat (Wistar)	2 yr 5 d/wk 7 hr/d		111			Torkelson et al. 1974

Table 3-1 Levels of Significant Exposure to 1,4-Dioxane - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Reproductive						
23	Rat (Wistar)	2 yr 5 d/wk 7 hr/d		111			Torkelson et al. 1974

a The number corresponds to entries in figure 3-1.

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 2.0 ppm for 1,4-dioxane; the MRL was derived by dividing the LOAEL by an uncertainty factor of 30 (3 for a minimal LOAEL and 10 to protect sensitive populations).

c Used to derive a chronic-duration inhalation minimal risk level (MRL) of 1.0 ppm for 1,4-dioxane; the NOAEL was converted to a human equivalent concentration of 35.5 ppm by using a PBPK model. The MRL was derived by dividing the NOAEL-HEC by an uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 to protect sensitive populations). The chronic duration inhalation MRL was adopted also as intermediate-duration MRL.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gastro = gastrointestinal; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to 1,4-Dioxane - Inhalation

Acute (≤14 days)

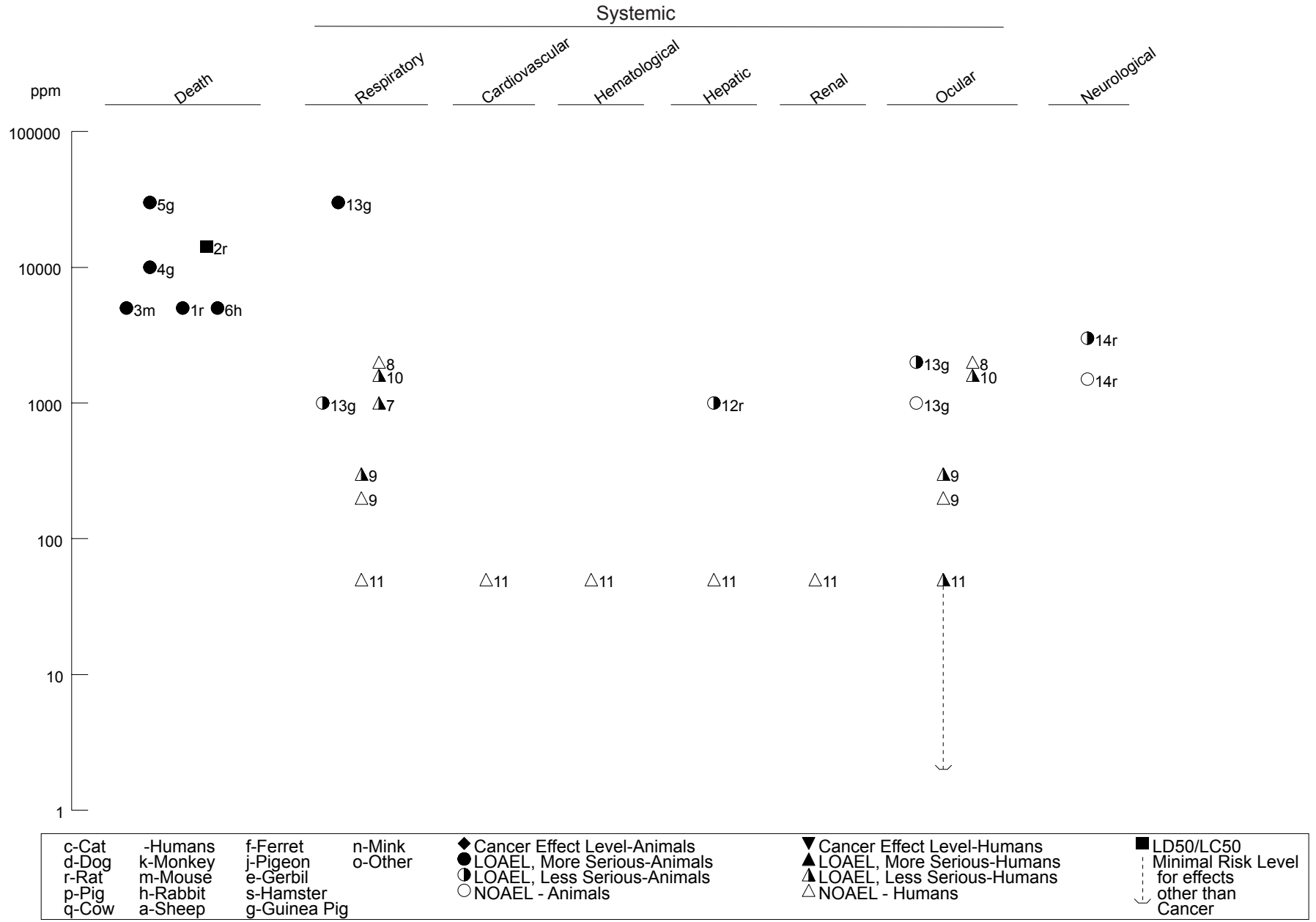


Figure 3-1. Levels of Significant Exposure to 1,4-Dioxane - Inhalation (*Continued*)

Intermediate (15-364 days)

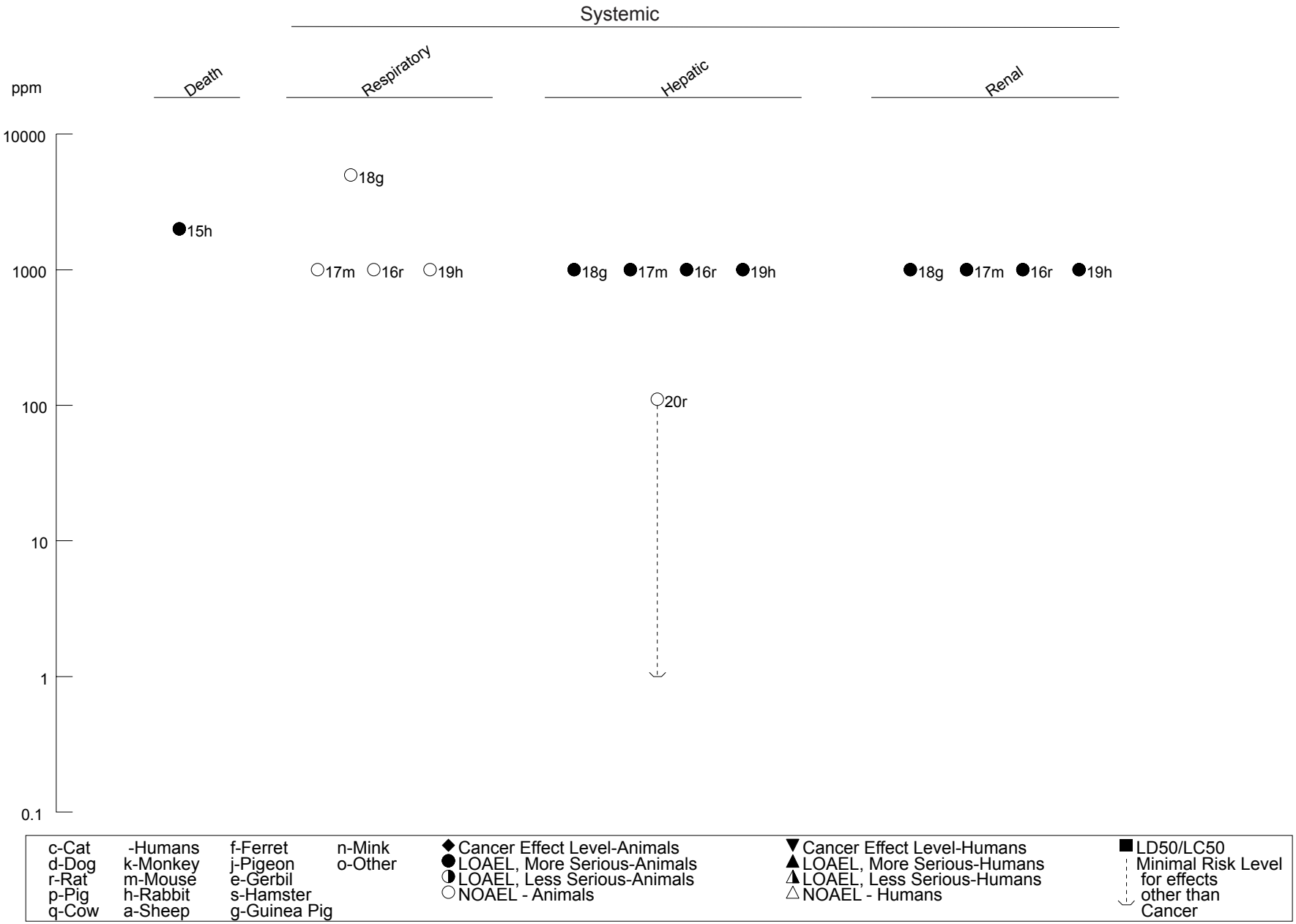
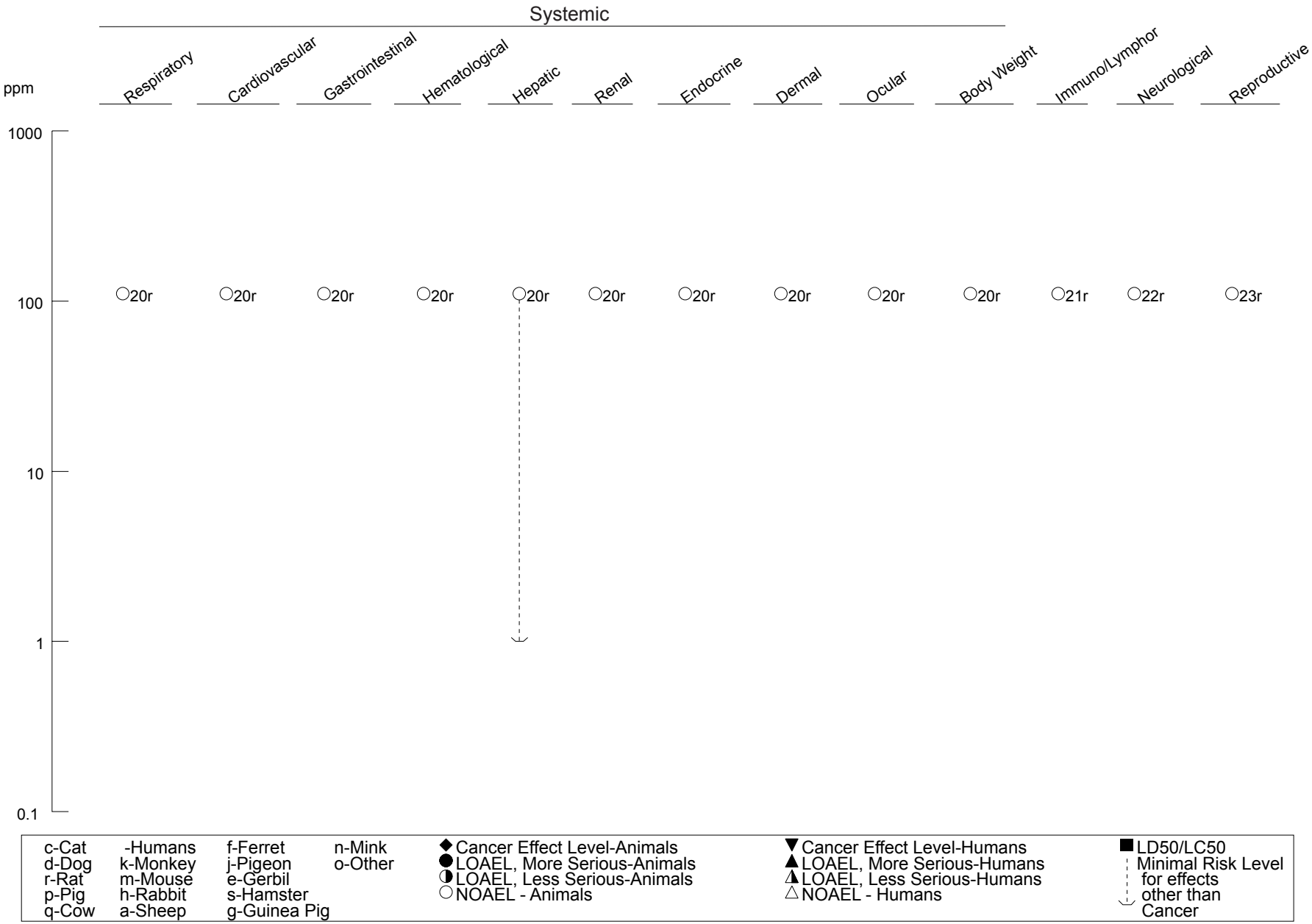


Figure 3-1. Levels of Significant Exposure to 1,4-Dioxane - Inhalation (*Continued*)

Chronic (=365 days)



In a study in guinea pigs exposed to 1,000–30,000 ppm 1,4-dioxane for periods ranging from 10 to 540 minutes, nasal irritation was evident almost immediately at all exposure levels (Yant et al. 1930). No respiratory changes were noticed with concentrations of up to 10,000 ppm for 480 minutes, but dyspnea and gasping occurred at 30,000 ppm for 45–116 minutes. The 30,000 ppm level caused death in the animals in about 180 minutes. Gross necropsy revealed exposure-duration-related hyperemia in the lungs. Surviving guinea pigs autopsied 8–10 days after exposure showed no gross pathological changes except for a few cases of hyperemic areas of congestion in the lungs. Exposure of rats and guinea pigs to acute lethal concentrations of 1,4-dioxane produced vascular congestion of the lungs (Fairley et al. 1934). No lung lesions were seen in rats, mice, or rabbits exposed to 1,000 ppm 1,4-dioxane for 3–12 weeks or in guinea pigs exposed to 5,000 ppm for the same duration (Fairley et al. 1934). In the 2-year inhalation study in rats by Torkelson et al. (1974), intermittent exposure to 111 ppm 1,4-dioxane caused no signs of nasal irritation, respiratory distress, or histopathologic alterations in the lungs and trachea of the animals.

Cardiovascular Effects. A study of four men exposed to 50 ppm 1,4-dioxane for 6 hours reported no abnormalities in the electrocardiograms (EKG) taken 24 hours and 2 weeks after exposure compared to EKGs taken prior to the study (Young et al. 1977); however, no data were provided in the study. High blood pressure was reported in subjects who eventually died following exposure to high amounts of 1,4-dioxane (Barber 1934; Johnstone 1959), but this may have been a non-specific response to a stressful condition or due to acute renal failure.

The only available information in animals is that no gross or histopathological alterations were observed in the heart from rats exposed to 111 ppm 1,4-dioxane for 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974).

Gastrointestinal Effects. Abdominal pain and vomiting were common features among subjects after exposure to high concentrations of 1,4-dioxane who eventually died (Barber 1934; Johnstone 1959). Barber (1934) suggested that the abdominal pain may have been due to stretching of the capsule of the liver and kidneys. No gross or histologic alterations were observed in the gastrointestinal tract from rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974).

Hematological Effects. A study of four male volunteers exposed to 50 ppm 1,4-dioxane for 6 hours reportedly did not show any significant effect of exposure on hematology parameters (Young et al. 1977); however, no data were provided in the study. Blood was collected prior to exposure and 24 hours and

2 weeks after exposure and subjected to a complete hematological analyses. Leukocytosis and eosinophilia were described in subjects who survived exposure to high concentrations of 1,4-dioxane described by Barber (1934). A cross-sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years found no significant alterations in hemoglobin concentration, erythrocyte counts, and total and differential leukocyte counts among the subjects (Thiess et al. 1976).

In the 2-year inhalation study in rats by Torkelson et al. (1974), hematological parameters were measured in blood collected after 16 and 23 months of exposure. In this study, the rats were exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week. The specific hematological parameters measured were packed corpuscular volume, erythrocyte counts, hemoglobin concentration, and total and differential leukocyte counts. No toxicologically significant deviations from normal limits were found.

Hepatic Effects. Short-term exposure of humans to concentrations that eventually caused death produced serious liver damage. Barber (1934) described five lethal cases in which postmortem examination of the patients revealed an enlarged liver and centrilobular necrosis of the liver cells. Similar lesions were observed in a lethal case described by Johnstone (1959). Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours produced no liver alterations as judged by standard clinical chemistry tests (although not specified) and triglyceride determination (Young et al. 1977). A cross sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years found no conclusive evidence of serious liver damage (Thiess et al. 1976). Although 6 out of 24 current workers had elevated serum transaminase levels, all 6 were known as habitual alcohol drinkers.

Guinea pigs exposed to acute lethal concentrations of 1,4-dioxane had liver lesions ranging from cloudy swelling to areas of complete necrosis (Fairley et al. 1934). The effect of 1,4-dioxane on the levels of serum ALT, AST, ornithine carbamyl transferase (OCT), and glucose-6-phosphatase was studied in groups of male rats exposed to 0, 1,000, or 2,000 ppm 1,4-dioxane for 4 hours (Drew et al. 1978). The enzyme levels were used as indication of liver damage. Exposure to 1,4-dioxane markedly increased the activities (concentration-related) of AST, ALT, and OCT, particularly 48 hours after exposure. The activity of glucose-6-phosphatase was slightly increased 48 hours after exposure.

A study in which rats, mice, guinea pigs, and rabbits were exposed to 1,000 ppm (the lowest concentration tested) 3 hours/day, 5 days/week for 3–12 weeks reported hepatocyte degeneration of

varying severity in all of the species tested (Fairley et al. 1934). In the 2-year inhalation bioassay in rats exposed intermittently to 111 ppm 1,4-dioxane, there was no evidence of any exposure-related gross or microscopic liver alterations or alterations in serum AST and alkaline phosphatase activities (Torkelson et al. 1974). The NOAEL of 111 ppm was used to derive a chronic-duration inhalation MRL of 1 ppm for 1,4-dioxane.

Renal Effects. Swollen kidneys with hemorrhage was commonly seen in subjects who died following exposure to unknown amounts of 1,4-dioxane in the air described by Barber (1934). Microscopic examination showed hemorrhage around the glomeruli with some necrosis. Barber (1934) stated that in at least three of the five cases he described, kidney disease was the direct cause of death. In a fatal case described by Johnstone (1959), postmortem examination revealed necrosis in the kidney cortex with extensive interstitial hemorrhage. Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours reportedly produced no kidney alterations as assessed by comparing serum creatinine values and urinalysis results obtained prior to exposure with results obtained 24 hours and 2 weeks after exposure (Young et al. 1977). No evidence of kidney damage was found in a cross-sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years (Thiess et al. 1976).

Kidney lesions were commonly observed in rodents exposed to acute lethal concentrations of 1,4-dioxane (Fairley et al. 1934). Examination of rats, mice, guinea pigs, and rabbits exposed to 1,000 ppm 1,4-dioxane (the lowest concentration tested) 3 hours/day, 5 days/week for 3–12 weeks, showed varying degrees of kidney damage ranging from vascular congestion to renal cortex degeneration (Fairley et al. 1934). In general, exposure to higher concentrations increased the severity of the effects. In a 2-year inhalation study in rats exposed intermittently to 111 ppm 1,4-dioxane, there were no treatment-related gross or microscopic alterations in the kidneys or significant alterations in blood-urea nitrogen and total protein concentration (Torkelson et al. 1974).

Endocrine Effects. No gross or microscopic alterations were observed in the thyroid and pituitary glands from rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). No further relevant information was located.

Dermal Effects. In the 2-year study in rats by Torkelson et al. (1974), the investigators indicated that intermittent exposure to a concentration of 111 ppm 1,4-dioxane in the air had no significant effect on skin condition; no microscopic examination of the skin was conducted. Had skin condition been affected,

it would have been most likely due to direct contact with the chemical rather than due to inhaled 1,4-dioxane.

Ocular Effects. In a group of six individuals exposed to 2,000 ppm 1,4-dioxane vapors for 3 minutes in a 10-m^3 chamber, there were no complaints of ocular discomfort (Fairley et al. 1934). Exposure to 300 ppm 1,4-dioxane for 15 minutes produced eye irritation among a group of 12 volunteers (Silverman et al. 1946). A 10-minute exposure to 1,600 ppm 1,4-dioxane produced slight eye irritation and lacrimation that persisted throughout the test in a groups of five individuals (Yant et al. 1930). In another experiment by the same investigators, exposure of the same five persons to 5,500 ppm 1,4-dioxane for 1 minute resulted in irritation of the eyes (Yant et al. 1930). Eye irritation throughout exposure was a frequent and the only complaint among four men exposed to 50 ppm for 6 hours in a study by Young et al. (1977). It is assumed that, in these cases, the irritation was caused by direct contact of the vapor with the eyes. The LOAEL of 50 ppm from the study by Young et al. (1977) was used to derive an acute-inhalation MRL of 2 ppm for 1,4-dioxane.

In a study in guinea pigs exposed to 1,000–30,000 ppm 1,4-dioxane for 10–540 minutes, eye irritation was observed at 2,000 ppm for 5 minutes and 3,000 ppm for 8 minutes, but not at 1,000 ppm for 480 minutes (Yant et al. 1930). No evidence of eye irritation was observed in rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years, but no histological examination of the eyes was performed (Torkelson et al. 1974).

Body Weight Effects. No significant effect on body weight gain was observed in rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). No further relevant information was located.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following inhalation exposure to 1,4-dioxane. No gross or microscopic alterations were observed in lymph nodes or the spleen from rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). This value is presented as a NOAEL for lymphoreticular effects in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Edema of the brain was observed in three of the five fatal cases described by Barber (1934). However, as suggested by NIOSH (1977), these changes were probably terminal, rather than specific toxic effects of 1,4-dioxane. Also, brain damage, possibly secondary to anoxia and cerebral edema, was observed in a worker who died following combined inhalation and dermal exposure to a high amount of 1,4-dioxane (Johnstone 1959). Postmortem examination showed moderate perivascular widening of the brain and demyelination and partial loss of nerve fiber in small areas of the basal nuclei.

Exposure of rats to ≥3,000 ppm 1,4-dioxane 4 hours/day 5 days/week for 2 weeks resulted in depression of an avoidance response (Goldberg et al. 1964). The maximal effect was obtained after the second day of exposure. All of the effects on behavior were reversible. Exposure of rats to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years caused no significant gross or microscopic alterations in the brain (Torkelson et al. 1974). Although only the brain was evaluated by Torkelson et al. (1974), the rats were observed throughout the study for signs of toxicity, including activity and demeanor; therefore, the value of 111 ppm is presented as a NOAEL for neurological effects in Table 3-1 and is plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to 1,4-dioxane. No alterations were observed in the reproductive organs from male (testes) and female (ovaries, oviduct, uterus, and vagina) rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). This NOAEL is presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or in animals following inhalation exposure to 1,4-dioxane.

3.2.1.7 Cancer

Limited information exists regarding exposure to 1,4-dioxane and cancer in humans. Thiess et al. (1976) conducted a cross-sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years. Twelve deaths had been reported and two were attributed to cancer, but the overall death rate and the cancer death rate were not significantly different than expected rates. An additional occupational study of 165 workers exposed intermittently to concentrations of 1,4-dioxane between 0.1 and 17 ppm (the maximums ranged between 1.5 and 3.2 ppm) at least one month during a 21-year period to found no significant differences between observed and expected incidences of cancer (Buffler et al. 1978). However, the study was limited in power to detect an effect due to the small size of the cohort, low levels of exposure, and the relatively short exposures.

No evidence of carcinogenicity due to 1,4-dioxane was found in a study in Wistar rats (288/sex) in which the animals were exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). A group of 192 rats/sex served as controls, and the evaluation included all major tissues and organs including the liver and nasal cavity.

3.2.2 Oral Exposure

3.2.2.1 Death

No reports of death in humans following oral exposure to 1,4-dioxane were found in the literature reviewed. Studies in animals have reported lethal doses in various species. Reported single dose LD_{50} values in rats include 5,346 mg/kg (Laug et al. 1939), 6,369 mg/kg (Pozzani et al. 1959), and 7,120 mg/kg (Smyth et al. 1941). Laug et al. (1939) also reported an LD_{50} of 5,852 mg/kg in mice and 4,033 mg/kg in guinea pigs. Two of 10 female rats dosed with 2,750 mg 1,4-dioxane/kg/day for 2 weeks in the drinking water died before the end of the study (JBRC 1998a). Smyth et al. (1941) calculated an LD_{50} of 3,150 mg/kg in guinea pigs, whereas de Navasquez (1935) reported 100% lethality in a group of five rabbits within 6 days of administration of a single dose of 2,068 mg of 1,4-dioxane/kg by gavage in water; a lower dose of 1,034 mg/kg was not lethal but produced narcolepsy, and doses of 207 mg/kg repeated at weekly intervals did not appear to affect the animals. All 10 female mice dosed with 3,230 mg 1,4-dioxane/kg/day in the drinking water died, and 9 of 10 males dosed with 3,630 mg/kg/day also died (JBRC 1998a). In a study using three dogs, consumption of approximately 327 mg

1,4-dioxane/kg/day via the drinking water killed one dog in 10 days, and consumption of approximately 375 mg/kg/day was lethal to an additional dog in 9 days (Schrenk and Yant 1936). Upon necropsy, common features in these animals were severe kidney and liver lesions consisting of cellular degeneration of the renal cortex and hemorrhages and vascular congestion in the kidneys and cellular degeneration in the liver. Because the dogs were allowed to drink the 1,4-dioxane solution only twice daily and no other source of water was available, dehydration may have played a role in their death.

In an intermediate-duration study, five of six rats dosed through drinking water that provided approximately 1,000 mg 1,4-dioxane/kg/day died between the 14th and 35th day of the study (Fairley et al. 1934). Necropsy of these animals revealed kidney and liver lesions. In a 2-year cancer bioassay in Sherman rats, significant early mortality beginning at about 2–4 months in the study was observed in males and females treated with 1,015 and 1,599 mg 1,4-dioxane/kg/day, respectively, in the drinking water (Kociba et al. 1974). Although the specific cause of death was not discussed, the investigators indicated that rats dying early showed degenerative changes in the liver and kidneys. Early mortality also was reported in other long-term studies in rats given ≥240 mg 1,4-dioxane/kg/day in the drinking water for 104–110 weeks (NCI 1978), or 398–514 mg/kg/day for 2 years (JBRC 1998c) and in mice treated similarly with ≥380 mg/kg/day for 90–104 weeks (NCI 1978) or ≥323 mg/kg/day for 2 years (JBRC 1998c). In the JBRC (1998c) study, early death in rats was attributed to liver and nasal cavity tumors and death in mice was attributed to liver tumors.

The LOAEL values for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, and body weight effects in humans after oral exposure to 1,4-dioxane.

The highest NOAEL and all reliable LOAEL values from each study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer- 344)	2 wk ad libitum (W)				2750 F (2/10 deaths)	JBRC 1998a
2	Rat (NS)	12 d (W)				1034 (8/10 deaths within 12 days)	Kesten et al. 1939
3	Rat (NS)	once (G)				5346 (LD50)	Laug et al. 1939
4	Rat (Wistar)	once (G)				6369 F (LD50)	Pozzani et al. 1959
5	Rat (Wistar)	once (GW)				7120 (LD50)	Smyth et al. 1941
6	Mouse (B6C3F1)	2 wk ad libitum (W)				3230 F (10/10 deaths)	JBRC 1998a
7	Mouse (NS)	once (G)				5852 (LD50)	Laug et al. 1939

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
8	Gn Pig (NS)	once (G)				4033 (LD50)	Laug et al. 1939
9	Gn Pig (NS)	once (GW)				3150 (LD50)	Smyth et al. 1941
10	Rabbit (NS)	once (GW)				2068 (5/5 deaths in 2-6 days)	De Navasquez 1935
	Systemic						
11	Rat (Fischer- 344)	2 wk ad libitum (W)	Resp	370[b] M	1010 M (nuclear enlargement of olfactory epithelium)		JBRC 1998a
			Hepatic	1040 F	2750 F (hepatocyte swelling and vacuolation)		
			Renal	1040 F	2750 F (hydropic change in proximal tubule)		
			Bd Wt	1040 F		2750 F (24% reduced body weight gain)	

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
12	Rat (NS)	12 d (W)	Hepatic		1034 (unspecified liver abnormalities)		Kesten et al. 1939
			Renal			1034 (kidney degeneration)	
13	Rat (Sprague-Dawley)	once (GW)	Hepatic	1000 M			Stott et al. 1981
14	Mouse (B6C3F1)	2 wk ad libitum (W)	Hepatic	1380 M	2550 M (swelling of central area)		JBRC 1998a
			Bd Wt	1380 M	2550 M (swelling of central area)		
	Neurological						
15	Rat (Fischer- 344)	2 wk ad libitum (W)		1040 F		2750 F (vacuolar changes in the brain)	JBRC 1998a
16	Rabbit (NS)	once (GW)		207		1034 (narcolepsy, slow gate, ataxia)	De Navasquez 1935

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
17	Rabbit (NS)	once (G)		1760	4400	(staggering)	6600	(narcosis)	Knoefel 1935
	Developmental								
18	Rat (Sprague-Dawley)	9 d Gd 6-15 (GW)		516	1033	(decreased fetal weight; reduced sternum ossification)			Giavini et al. 1985
	INTERMEDIATE EXPOSURE								
	Death								
19	Rat (NS)	34 d ad libitum (W)					1000	(5/6 deaths before the 35th day)	Fairley et al. 1934
20	Rat (Sherman)	2-4 mo ad libitum (W)					1015 M	(significant early mortality beginning at 2 months in the study)	Kociba et al. 1974
	Systemic								
21	Rat (NS)	34 d ad libitum (W)	Gastro		1428	(gastroenteritis)			Fairley et al. 1934
			Hepatic				1428	(hepatocyte degeneration)	
			Renal				1428	(renal cortex degeneration)	

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
22	Rat (Fischer- 344)	13 wk ad libitum (W)	Resp	60 M	150 M (nuclear enlargement of respiratory epithelium)		JBRC 1998b
			Cardio	2020 F			
			Gastro	2020 F			
			Hemato	760 M	1900 M (increased red blood cell, hemoglobin, hematocrit, neutrophils)		
			Musc/skel	2020 F			
			Hepatic	60[c] M	150 M (swelling in central area)		
			Renal	330 M	760 M (nuclear enlargement of proximal tubule)		
				100[d] F	200[d] F (increased kidney weight)		
			Endocr	2020 F			
			Dermal	2020 F			
			Ocular	2020 F			
			Bd Wt	430 M	870 F (12% reduction in weight gain)	2020 F (21% reduction in body weight gain)	

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
23	Rat (Sprague-Dawley)	7 wk 5 d/wk (GW)	Hepatic	100 M	1000 M (fatty vacuoles in cytoplasm of hepatocytes)		Lundberg et al. 1987
24	Rat (Sprague-Dawley)	11 wk ad libitum (W)	Hepatic	10 M	1000 M (minimal hepatocellular swelling)		Stott et al. 1981
			Bd Wt	1000 M			
25	Mouse (NS)	67 d ad libitum (W)	Hepatic			2916 (hepatocyte degeneration)	Fairley et al. 1934
			Renal			2916 (cell degeneration in renal cortex)	

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Mouse (B6C3F1)	13 wk ad libitum (W)	Resp	170 F	410 F (nuclear enlargement of bronchial epithelium)		JBRC 1998b
			Cardio	2700 F			
			Gastro	2700 F			
			Hemato	920 M	1830 M (increase red blood cell, hemoglobin, hematocrit, corpuscular volume)		
			Musc/skel	2700 F			
			Hepatic	260 M	580 M (single cell necrosis and swelling of central area)		
			Renal	1710 F	2700 F (increased relative kidney weight)		
			Endocr	2700 F			
			Dermal	2700 F			
			Ocular	2700 F			
			Bd Wt	920[d] M		1830 M (29% reduced body weight gain)	
				2700 F			

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immuno/ Lymphoret						
27	Rat (Fischer- 344)	13 wk ad libitum (W)		2020 F			JBRC 1998b
28	Mouse (B6C3F1)	13 wk ad libitum (W)		2700 F			JBRC 1998b
	Neurological						
29	Rat (Fischer- 344)	13 wk ad libitum (W)		760 M		1900 M (vacuolar changes in the brain)	JBRC 1998b
30	Mouse (B6C3F1)	13 wk ad libitum (W)		2700 F			JBRC 1998b
	Reproductive						
31	Rat (Fischer- 344)	13 wk ad libitum (W)		1900 M[d] 2020 F			JBRC 1998b

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
32	Mouse (B6C3F1)	13 wk ad libitum (W)		1830[d] M 2700 F			JBRC 1998b
	CHRONIC EXPOSURE						
	Death						
33	Rat (Fischer- 344)	2 yr ad libitum (W)				398 M (increased early mortality)	JBRC 1998c
34	Rat (Osborne-Mendel)	110 wk ad libitum (W)				240 M (early mortality)	NCI 1978
35	Mouse (B6C3F1)	2 yr ad libitum (W)				323 F (increased early mortality)	JBRC 1998c
36	Mouse (B6C3F1)	90 wk ad libitum (W)				380 F (early mortality)	NCI 1978

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
37	Rat (Wistar)	452 d ad libitum (W)	Renal		584 M (glomerulonephritis)		Argus et al. 1965

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (Fischer- 344)	2 yr ad libitum (W)	Resp	21 F	103 F (nuclear enlargement of olfactory epithelium)		JBRC 1998c
			Cardio	514 F			
			Gastro	514 F			
			Hemato	16 M	81 M (decreased erythocytes, hemoglobin, hematocrit)		
			Musc/skel	514 F			
			Hepatic	16 M	81 M (liver hyperplasia, spongiosis, clear cell foci)		
			Renal	21 F	103 F (blood in the urine; nuclear enlargement of proximal tubule)		
			Endocr	514 F			
			Dermal	514 F			
			Ocular	514 F			
			Bd Wt	81 M	398 M (10% reduced body weight gain)		

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Rat (Sherman)	716 d ad libitum (W)	Resp	1599 F			Kociba et al. 1974
			Cardio	1599 F			
			Gastro	1599 F			
			Hemato	1599 F			
			Hepatic	9.6[e] M			
				94 M			
			Renal	9.6 M	94 M (degeneration and necrosis of tubular epithelium)		
			Endocr	1599 F			
			Bd Wt	94 M	1015 M (>10% reduced weight gain)		

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
40	Rat (Osborne-Mendel)	110 wk ad libitum (W)	Resp		240 M (increased incidence of pneumonia)		NCI 1978
			Cardio	640 F			
			Gastro		240 M (stomach ulcers)		
			Musc/skel	640 F			
			Hepatic	240 M	350 F (hepatocytomegaly)		
			Renal			240 M (cortical tubular degeneration)	
			Endocr	640 F			
			Dermal	640 F			
			Bd Wt	240 M	530 M (reduced body weight gain, unquantified)		

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Mouse (B6C3F1)	2 yr ad libitum (W)	Resp	66 M	251 M (nuclear enlargement of olfactory epithelium in nasal cavity)		JBRC 1998c
			Cardio	1066 F			
			Gastro	1066 F			
			Hemato	77 F	323 F (reduced blood platelets)		
			Musc/skel	1066 F			
			Hepatic	66 M	251 M (increased serum AST, ALT, AP, and LDH activities)		
			Renal	77 F	323 F (increased protein, glucose, and blood in urine)		
			Endocr	1066 F			
			Dermal	1066 F			
			Ocular	1066 F			
			Bd Wt	251 M 77 F[d]	323 F (15% reduced body weight gain)	768 M (43% reduced body weight gain)	

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
42	Mouse (B6C3F1)	90 wk ad libitum (W)	Resp		380 F (increased incidence of pneumonia)		NCI 1978
			Cardio	860 F			
			Gastro	860 F			
			Musc/skel	860 F			
			Hepatic	860 F			
			Renal	860 F			
			Endocr	860 F			
			Dermal	860 F			
			Bd Wt	830 M 380 F[d]	860 F (decreased body weight gain, unquantified)		
	Immuno/ Lymphoret						
43	Rat (Fischer- 344)	2 yr ad libitum (W)		514 F			JBRC 1998c

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
44	Rat (Sherman)	716 d ad libitum (W)		1599 F			Kociba et al. 1974
45	Rat (Osborne-Mendel)	110 wk ad libitum (W)		640 F			NCI 1978
46	Mouse (B6C3F1)	2 yr ad libitum (W)		1066 F			JBRC 1998c
47	Mouse (B6C3F1)	90 wk ad libitum (W)		860 F			NCI 1978
	Neurological						
48	Rat (Fischer- 344)	2 yr ad libitum (W)		514 F			JBRC 1998c
49	Rat (Sherman)	716 d ad libitum (W)		1599 F			Kociba et al. 1974

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
50	Rat (Osborne-Mendel)	110 wk ad libitum (W)		640 F			NCI 1978
51	Mouse (B6C3F1)	2 yr ad libitum (W)		1066 F			JBRC 1998c
52	Mouse (B6C3F1)	90 wk ad libitum (W)		860 F			NCI 1978
	Reproductive						
53	Rat (Fischer- 344)	2 yr ad libitum (W)		514 F			JBRC 1998c
54	Rat (Sherman)	716 d ad libitum (W)		1599 F			Kociba et al. 1974
55	Rat (Osborne-Mendel)	110 wk ad libitum (W)		640 F			NCI 1978

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
56	Mouse (B6C3F1)	2 yr ad libitum (W)		1066 F			JBRC 1998c
57	Mouse (B6C3F1)	90 wk ad libitum (W)		860 F			NCI 1978
	Cancer						
58	Rat (Wistar)	452 d ad libitum (W)				584 M (CEL: liver tumors)	Argus et al. 1965
59	Rat (Fischer- 344)	2 yr ad libitum (W)				398 M (CEL: combined squamous cell carcinoma, sarcoma, rhabdomyosarcoma, esthesioneuroepithelioma of nasal cavity; hepatocallular carcinoma and sarcoma of the liver; mesothelioma of the peritoneum)	JBRC 1998c

[a] Key to figure

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
60	Rat (Sherman)	716 d ad libitum (W)				1015 M (CEL: hepatocellular carcinomas)	Kociba et al. 1974
61	Rat (Osborne-Mendel)	110 wk ad libitum (W)				350 F (CEL:hepatocellular carcinomas) 240 (CEL: nasal carcinomas in both sexes)	NCI 1978
62	Mouse (B6C3F1)	2 yr ad libitum (W)				77 F (CEL: hepatocellular adenomas and carcinomas)	JBRC 1998c
63	Mouse (B6C3F1)	90 wk ad libitum (W)				380 F (CEL: increased incidence of hepatocellular carcinomas and adenomas)	NCI 1978

Table 3-2 Levels of Significant Exposure to 1,4-Dioxane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
64	Gn Pig (NS)	23 mo ad libitum (W)				1014 M (CEL: increased incidence of hepatomas)	Hoch-Ligeti and Argus 1970

a The number corresponds to entries in figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 4.0 mg/kg/day for 1,4-dioxane; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 animal to human extrapolation and 10 to protect sensitive populations).

c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day for 1,4-dioxane; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 animal to human extrapolation and 10 to protect sensitive populations).

d Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

e Used to derive a chronic-duration oral minimal risk level (MRL) of 0.1 mg/kg/day for 1,4-dioxane; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 animal to human extrapolation and 10 to protect sensitive populations)

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GW) = gavage in water; hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)

Figure 3-2. Levels of Significant Exposure to 1,4-Dioxane - Oral

Acute (≤14 days)

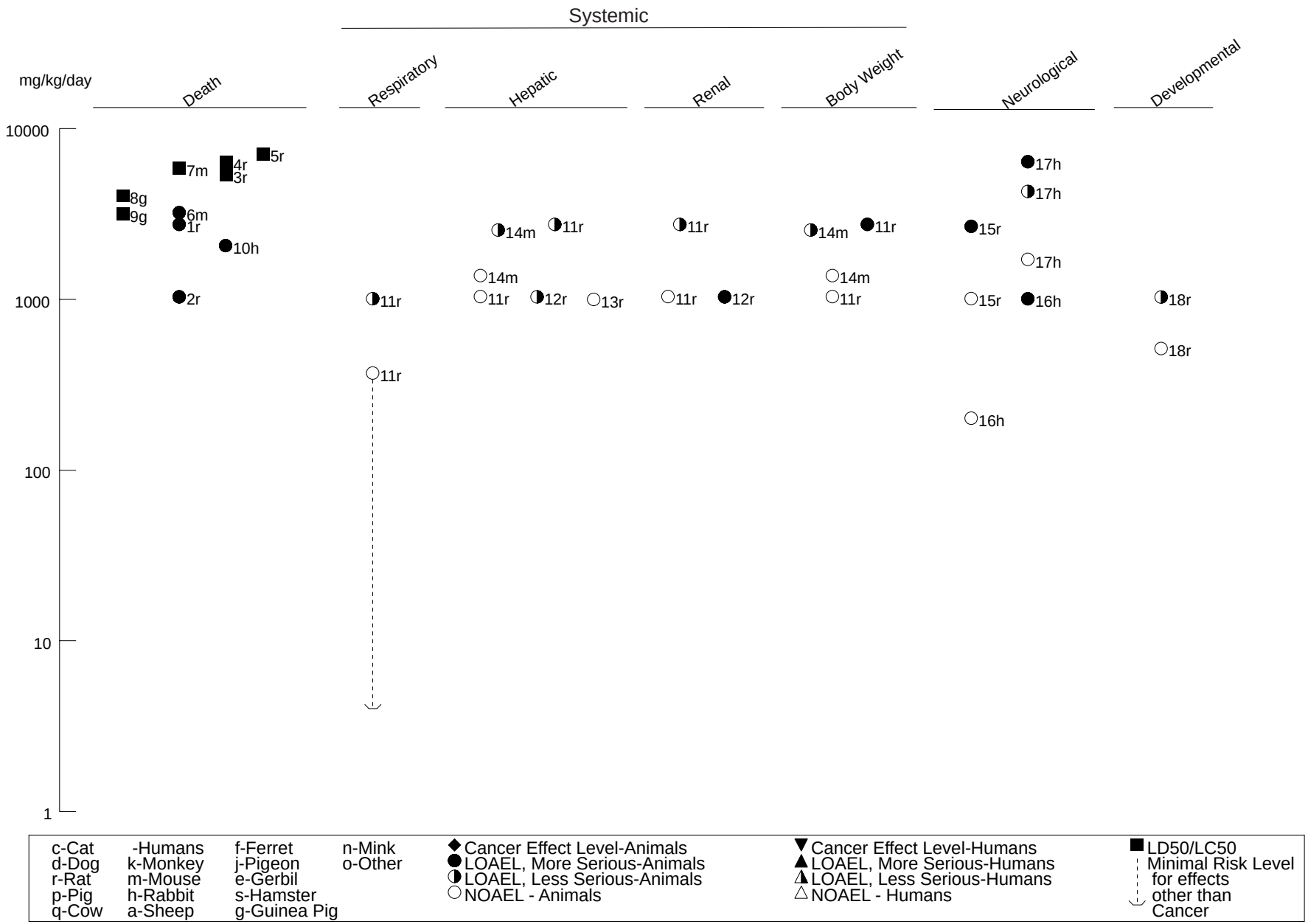


Figure 3-2. Levels of Significant Exposure to 1,4-Dioxane - Oral (*Continued*)

Intermediate (15-364 days)

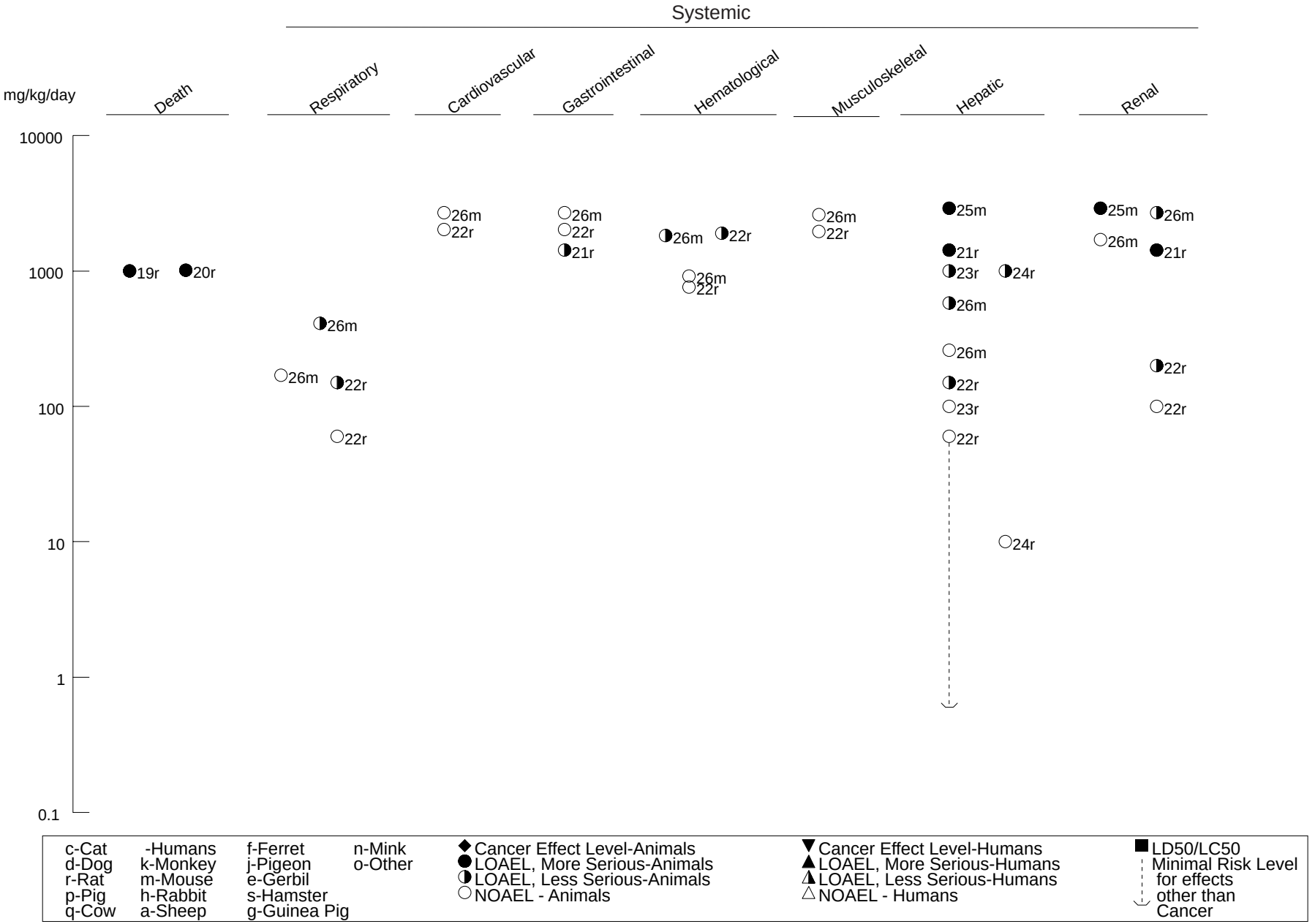


Figure 3-2. Levels of Significant Exposure to 1,4-Dioxane - Oral (*Continued*)

Intermediate (15-364 days)

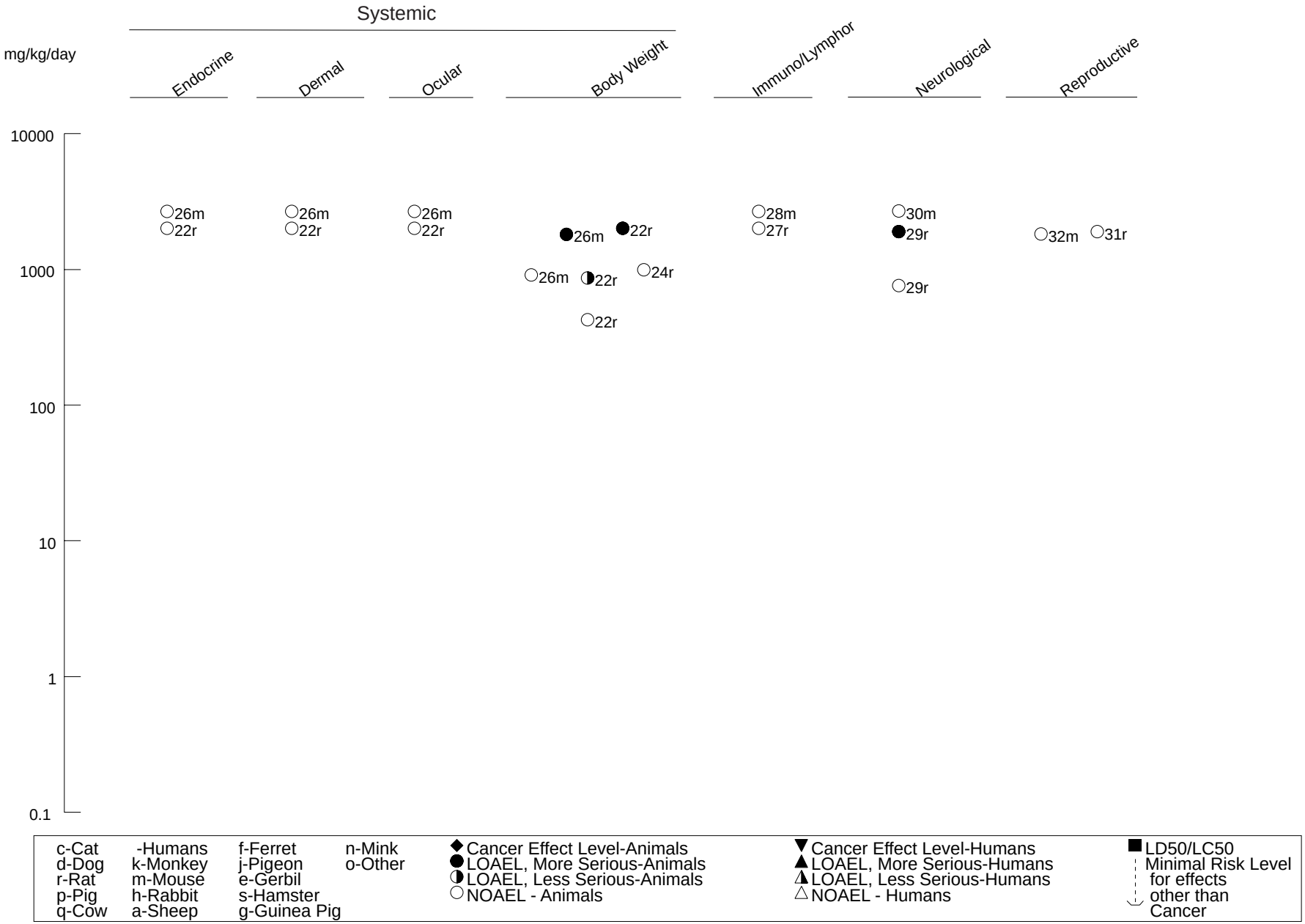


Figure 3-2. Levels of Significant Exposure to 1,4-Dioxane - Oral (*Continued*)

Chronic (≥365 days)

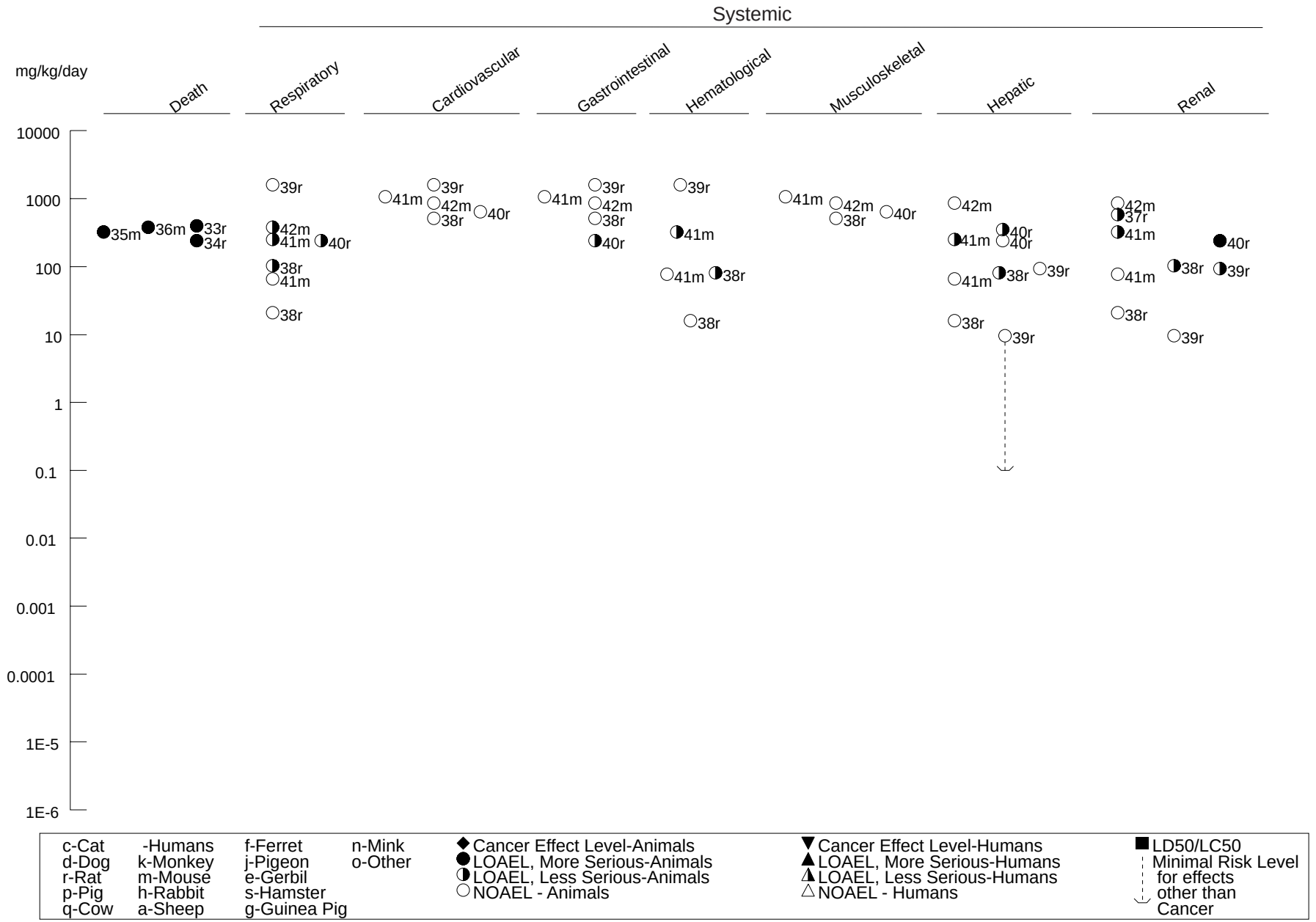
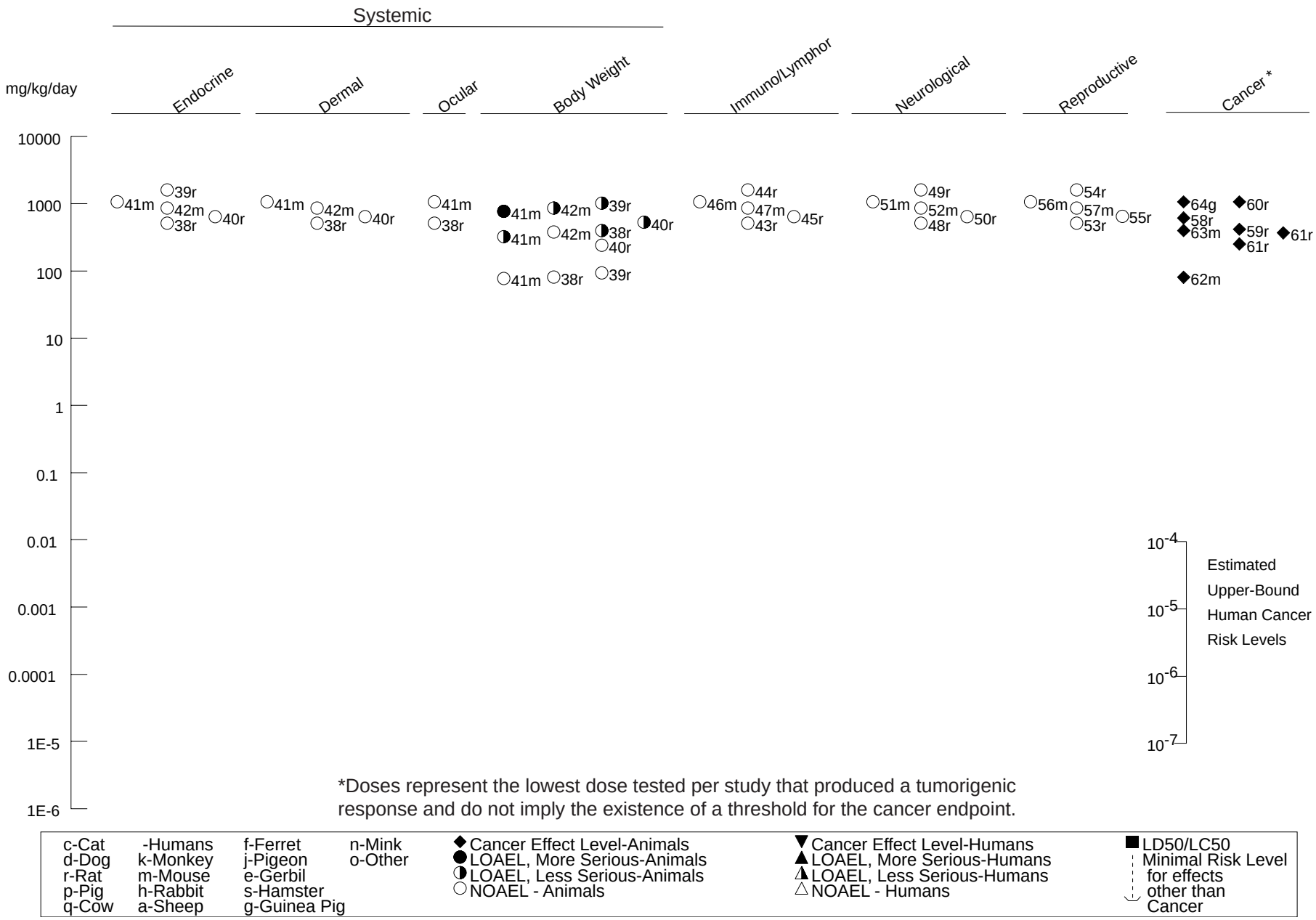


Figure 3-2. Levels of Significant Exposure to 1,4-Dioxane - Oral (*Continued*)

Chronic (≥365 days)



Respiratory Effects. Information exists regarding nasal and respiratory effects in animals after oral exposure to 1,4-dioxane. Nuclear enlargement of the olfactory epithelium was observed in male and female F344/DuCrj rats dosed with 1,010 and 1,040 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 2 weeks (JBRC 1998a); the respective NOAELs were 370 and 400 mg/kg/day. The same type of lesions were observed in male and female rats treated with 150 and 200 mg 1,4-dioxane/kg/day, respectively, for 13 weeks; the respective NOAELs were 60 and 100 mg/kg/day (JBRC 1998b). The nasal effects in rats described by JBRC (1998a) were used to derive an acute-duration oral MRL of 4 mg/kg/day for 1,4-dioxane. Male and female Crj:BDF_1 mice dosed with 580 and 410 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks showed nuclear enlargement of the bronchial epithelium; higher doses also involved the nasal cavity, trachea, and lungs (JBRC 1998b); the respective NOAELs were 260 and 170 mg/kg/day. No histopathologic changes were observed in the lungs and nasal turbinates from Sherman rats dosed with up to 1,599 mg 1,4-dioxane/kg/day in the drinking water for 716 days (Kociba et al. 1974). No significant non-neoplastic lesions were seen in the lungs and trachea from Osborne-Mendel rats dosed with up to 640 mg 1,4-dioxane/kg/day via drinking water for 110 weeks (NCI 1978). However, an increased incidence of pneumonia was seen in treated males and females, although the incidence was not dose-related. The investigators speculated that the development of nasal carcinomas might have been a contributing factor (NCI 1978). Female Fischer 344 rats dosed with approximately 103 mg 1,4-dioxane/kg/day, also in the drinking water, for 104 weeks showed a nuclear enlargement of the olfactory epithelium in the nasal cavity, the NOAEL was 21 mg/kg/day (JBRC 1998c). In males, nasal cavity lesions were observed at 398 mg/kg/day, and the NOAEL in males was 81 mg/kg/day.

In B6C3F_1 mice treated with 1,4-dioxane in the drinking water for 90 weeks, there was a dose-related increase in the incidence of pneumonia in males and females and of rhinitis in females (NCI 1978); males were dosed with 720 or 830 mg/kg/day and females were dosed with 380 or 860 mg/kg/day. Examination of the lungs and trachea did not reveal any other treatment-related non-neoplastic alterations. Male Crj:BDF_1 mice dosed with 251 mg 1,4-dioxane/kg/day in the drinking water for 2 years showed nuclear enlargement of olfactory epithelium in the nasal cavity; the NOAEL was 66 mg/kg/day (JBRC 1998c). Higher doses also involved the tracheal and bronchial epithelium. In females, nasal and bronchial alterations were observed at ≥323 mg/kg/day.

Cardiovascular Effects. No gross or histological alterations were observed in the heart from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for

13 weeks (JBRC 1998b). Also, no gross or histological alterations were reported in the heart from rats dosed with up to 1,599 mg 1,4-dioxane/kg/day in the drinking water for 2 years (JBRC 1998c; Kociba et al. 1974; NCI 1978) or in mice dosed with up to 860 mg/kg/day for 90 weeks (NCI 1978) or 1,066 mg/kg/day for 2 years (JBRC 1998c).

Gastrointestinal Effects. Hemorrhage of the stomach was reported in rats, mice, guinea pigs, and dogs administered acute lethal doses of 1,4-dioxane by gavage (Laug et al. 1939; Schrenk and Yant 1936; Smyth et al. 1941). Gastroenteritis was also reported in rats that died after drinking water that provided approximately 1,428 mg 1,4-dioxane/kg/day for up to 34 days (Fairley et al. 1934). No gross or histological alterations were observed in the gastrointestinal tract from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), In chronic-duration studies, no gastrointestinal alterations were reported in Sherman rats dosed with up to 1,599 mg 1,4-dioxane/kg/day (Kociba et al. 1974), in F344/DuCrj rats dosed with up to 514 mg/kg/day (JBRC 1998c), in B6C3F_1 mice treated with up to 860 mg/kg/day (NCI 1978), or in Crj:BDF_1 mice dosed with up to 1,066 mg/kg/day (JBRC 1998c). However, male Osborne-Mendel rats treated with ≥240 mg/kg/day for 110 weeks developed stomach ulcers; no such lesions were seen in control males or in female rats (NCI 1978).

Hematological Effects. Hematological changes consisting of increased red blood cell counts, hemoglobin, and hematocrit were reported in F344/DuCrj male rats dosed with 1,900 mg 1,4-dioxane/kg/day in the drinking water for 13 weeks; no significant changes occurred at 760 mg/kg/day (JBRC 1998b). In females, there was a decrease in mean corpuscular volume and platelet concentration at 2,020 mg/kg/day. The same authors reported that male Crj:BDF_1 mice treated with 1,830 mg 1,4-dioxane/kg/day had increased red blood cell counts, hemoglobin, hematocrit, and mean corpuscular volume; the NOAEL was 920 mg/kg/day. Female mice only showed an increase in mean corpuscular volume at ≥1,710 mg/kg/day. Decreased red blood cell counts, hemoglobin, and hematocrit was reported in male and female F344/DuCrj rats treated with 81 and 514 mg 1,4-dioxane/kg/day, respectively, for 2 years in the drinking water (JBRC 1998c). The respective NOAELs were 16 and 103 mg/kg/day. However, Sherman rats showed no significant deviations from normality in hematological parameters in another 2-year study (Kociba et al. 1974). In the latter study, the rats were dosed with up to 1,599 mg 1,4-dioxane/kg/day in the drinking water; blood samples were collected during the 4^{th}, 6^{th}, 12^{th}, and 18^{th} month and at termination, and analyzed for packed cell volume, total erythrocyte counts, hemoglobin concentration, and total and differential white blood cell counts.

Male Crj:BDF_1 mice dosed with 768 mg 1,4-dioxane/kg/day in the drinking water for 2 years had increased red blood cell counts, hemoglobin, and hematocrit, whereas females exhibited a significant reduction in platelet concentration at ≥323 mg/kg/day (JBRC 1998c). The respective hematological NOAELs were 251 and 77 mg/kg/day.

Musculoskeletal Effects. No gross or histological alterations were observed in bone and skeletal muscle (neither specified) from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). Similarly, no histopathologic alterations were observed in skeletal muscle from rats dosed with up to 640 mg 1,4-dioxane/kg/day for 110 weeks or in mice treated with up to 860 mg/kg/day for 90 weeks (NCI 1978).

Hepatic Effects. Acute oral doses of 1,4-dioxane that caused lethality in rats, mice, rabbits, guinea pigs, and dogs (see Section 3.2.2.1) induced varying degrees of liver damage, including liver congestion and degeneration (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Schrenk and Yant 1936; Smyth et al. 1941). In general, single doses that caused death were higher than 2,000 mg/kg. A single dose of 1,000 mg/kg administered to rats, and that did not cause death, produced no histopathologic alterations in the liver (Stott et al. 1981). Hepatocyte swelling and vacuolation of the central area were reported in the liver from F344/DuCrj rats dosed with 2,750–2,960 mg 1,4-dioxane/kg/day for 2 weeks in the drinking water (JBRC 1998a), but no significant liver alterations were seen at 1,010–1,040 mg/kg/day. Crj:BDF_1 mice treated in the same manner with 2,550–3,230 mg 1,4-dioxane/kg/day showed single cell necrosis and swelling of the central area; no significant alterations were reported at 1,380–1,780 mg/kg/day (JRBC 1998a). Repeated administration of doses of approximately 1,428 mg 1,4-dioxane/kg/day in the drinking water for 34 days was lethal to rats and examination of the animals showed liver congestion and hepatocyte degeneration (Fairley et al. 1934). The same types of liver lesions were seen in mice treated in the same manner with approximately 2,916 mg 1,4-dioxane/kg/day; in this experiment, the mice survived up to day 67, at which time they were sacrificed (Fairley et al. 1934). Repeated dosing of rats with 1,000 mg 1,4-dioxane/kg/day for 7 or 11 weeks produced hepatocyte swelling and histopathology (Stott et al. 1981) and fatty vacuoles in the hepatocytes (Lundberg et al. 1987). Male F344/DuCrj rats dosed with ≥150 mg 1,4-dioxane/kg/day for 13 weeks in the drinking water showed swelling of the central area (JBRC 1998b); the NOAEL was 60 mg/kg/day. Higher doses also produced vacuolar changes and granulation, and changes in clinical chemistry parameters indicative of liver toxicity. In female rats, granulation was evident at 430 mg/kg/day and hepatocyte swelling at 870 mg/kg/day. The findings from the JBRC (1998b) study in rats were used to derive an intermediate-

duration oral MRL of 0.6 mg/kg/day for 1,4-dioxane using a NOAEL of 60 mg/kg/day for male rats. In Crj:BDF_1 mice treated in the same manner, doses of 580–920 mg 1,4-dioxane/kg/day caused single cell necrosis and swelling in the central area, but doses ≤410 mg/kg/day were without significant effect (JBRC 1998b). Changes in clinical chemistry parameters suggestive of liver damage were reported also in mice dosed with ≥580 mg 1,4-dioxane/kg/day (JBRC 1998b). In the 2-year bioassay by Kociba et al. (1974) in Sherman rats, significant early deaths occurred with doses between 1,015 and 1,599 mg/kg/day beginning at about 2–4 months in the study, and the authors indicated that these rats exhibited degenerative changes in the liver, although is was not made clear whether these changes along with renal lesions were the cause of death. Rats treated chronically with 1,4-dioxane in the drinking water (≥94 mg/kg/day for males, ≥148 mg/kg/day for females) had liver lesions consisting of various degrees of hepatocellular degeneration and necrosis and evidence of hepatic regeneration, as indicated by hepatocellular hyperplastic nodule formation (Kociba et al. 1974). No significant effects were seen in males at 9.6 mg/kg/day and in females at 19 mg/kg/day. The findings from Kociba et al. (1974) were used to derive a chronic-duration oral MRL of 0.1 mg/kg/day for 1,4-dioxane. An elevated incidence of hepatocytomegaly was observed in female rats treated with ≥350 mg 1,4-dioxane/kg/day (the lowest dose tested in females) and in males dosed with 530 mg/kg/day of the chemical in the drinking water for 2-years (NCI 1978); the NOAEL in males was 240 mg/kg/day. In another 2-year drinking water study in F344/DuCrj rats, liver hyperplasia, spongiosis, and cell foci developed in males dosed with ≥81 mg 1,4-dioxane/kg/day, but not with 16 mg/kg/day (JBRC 1998c). Females treated with 514 mg/kg/day also developed hyperplasia, spongiosis, and cell foci, but no such lesions were observed at 103 mg/kg/day.

Mice dosed with up to 860 mg 1,4-dioxane/kg/day via the drinking water for 90 weeks showed no treatment-related non-neoplastic liver lesions (NCI 1978). Although the investigators stated that hepatocytomegaly was commonly found in treated mice, the incidences were not significantly different than in controls and no trend was apparent. Crj:BDF_1 mice dosed with 251–323 mg 1,4-dioxane for 2 years had significantly increased serum transaminase activities, and no gross or histological alterations were reported in females treated with doses of up to 1,066 mg/kg/day of 1,4-dioxane (JBRC 1998c). However, male mice showed angiectasis (abnormal dilation of a blood vessel) in the liver at 768 mg/kg/day.

Renal Effects. Acute lethal doses of 1,4-dioxane in rodents caused kidney lesions ranging from kidney enlargement to extensive kidney degeneration (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Smyth et al. 1941). Severe kidney damage was seen also in an acute study in dogs (Schrenk and

Yant 1936). Hydropic changes of the proximal renal tubule were reported in male and female F344/DuCrj rats dosed with 2,960 and 2,750 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 2 weeks (JBRC 1998a); the corresponding NOAELs were 1,010 and 1,040 mg/kg/day. Treatment for 13 weeks resulted in nuclear enlargement of the proximal renal tubules at 760 and 870 mg 1,4-dioxane/kg/day in male and female rats, respectively (JBRC 1998b); higher doses also induced hydropic changes in the proximal tubules. The NOAELs for morphological alterations in the kidneys were 330 and 430 mg/kg/day in males and females, respectively. Other significant findings in this study were a decrease in urinary pH in males at ≥330 mg/kg/day and an increase in absolute and relative kidney weight in females at ≥200 mg/kg/day. In another study, rats dosed for up to 34 days with 1,428 mg 1,4-dioxane/kg/day, a dose that caused deaths, had vascular congestion in the kidneys and cell degeneration in the cortical epithelium (Fairley et al. 1934). Similar lesions were observed in mice treated in the same fashion with approximately 2,916 mg/kg for up to 67 days (Fairley et al. 1934). Changes resembling glomerulonephritis were reported in male Wistar rats exposed to approximately 584 mg 1,4-dioxane/kg/day in the drinking water for about 452 days (Argus et al. 1965). Treatment of female Crj:BDF_1 mice with 1,710 mg 1,4-dioxane/kg/day in the drinking water for 13 weeks increased absolute kidney weight and decreased urinary pH; urinary pH was decreased in males at 920 mg/kg/day. Doses of 580 and 920 mg/kg/day in males and females, respectively, did not cause any significant renal effects (JBRC 1998b).

Kociba et al. (1974) observed degenerative changes in the kidneys from Sherman rats that died after 2–4 months of drinking water that provided approximately 1,015 mg 1,4-dioxane to males and 1,599 mg/kg/day to females. At termination of this 2-year study, the kidneys of both males (≥94 mg/kg/day) and females (≥148 mg/kg/day) showed tubular epithelial degeneration and necrosis, and there was evidence of renal tubular regeneration as indicated by increased tubular epithelial regenerative activity. The NOAEL in males and females was 9.6 and 19 mg/kg/day, respectively (Kociba et al. 1974). In the NCI (1978) bioassay in Osborne-Mendel rats, kidney lesions consisting of vacuolar degeneration and/or focal tubular epithelial regeneration in the proximal cortical tubules and occasionally hyaline casts were seen with significantly higher incidence in treated males (≥240 mg/kg/day, dose-related) and in high-dose females (640 mg/kg/day). The pH of the urine was significantly decreased in male F344/DuCrj rats dosed with 398 mg 1,4-dioxane/kg/day in the drinking water for 2 years, but no change was observed at 81 mg/kg/day (JBRC 1998c). In females, treatment with 103 mg/kg/day resulted in the detection of blood in the urine, decreased urinary pH, and nuclear enlargement of the proximal tubules; the NOAEL for renal effects in females was 21 mg/kg/day.

No treatment-related kidney lesions were observed in $B6C3F_1$ mice treated via the drinking water with up to 860 mg 1,4-dioxane/kg/day for 90 weeks (NCI 1978). Similar treatment of male $Crj:BDF_1$ mice with 768 mg 1,4-dioxane/kg/day resulted in decreased pH of the urine and nuclear enlargement of the proximal tubule; no such changes were observed at 251 mg/kg/day (JBRC 1998c). In females, doses of 323 mg/kg/day induced the excretion of glucose and protein in the urine and hematuria, but no gross or histopathological alterations were reported with doses up to 1,066 mg/kg/day. The NOAEL for renal effects in females was 77 mg/kg/day.

Endocrine Effects. No gross or histological alterations were observed in endocrine (thyroid, parathyroid, adrenal, pituitary) and exocrine (pancreas, salivary) glands from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). No gross or microscopic alterations were seen in the pituitary, adrenal, thyroid, and parathyroid glands from rats dosed with up to 1,599 mg 1,4-dioxane/kg/day in the drinking water for 2 years (Kociba et al. 1974; NCI 1978) or in the same organs from mice dosed in the same manner with up to 860 mg 1,4-dioxane/kg/day (NCI 1978). No further information was located on effects of 1,4-dioxane on endocrine parameters.

Dermal Effects. No gross or histological alterations were observed in the skin from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). Treatment of rats with up to 640 mg 1,4-dioxane/kg/day in the drinking water for 2 years or mice with up to 860 mg 1,4-dioxane/kg/day had no significant effect on the gross or microscopic appearance of the skin (NCI 1978).

Ocular Effects. No gross or histological alterations were observed in the eyes from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). No other relevant information was located.

Body Weight Effects. Administration of a single dose of 10 mg 1,4-dioxane/kg by gavage in water to rats reduced body weight gain by approximately 32% relative to controls in a 7-day period (Stott et al. 1981). According to the investigators, this was likely due to a reduction in food consumption, consistent with the histological observation that hepatocytes were depleted of glycogen. However, treatment with

10 mg/kg/day for 11 weeks had no significant effect on weight gain, and doses of 1,000 mg/kg/day for 11 weeks decreased body weight only about 9% relative to controls (Stott et al. 1981). In 2-week drinking water studies, doses of approximately 2,750–2,960 mg 1,4-dioxane/kg/day reduced body weight gain in F344/DuCrj rats (JBRC 1998a). In Crj:BDF_1 mice, a significant reduction in body weight gain occurred in males at 2,550 mg/kg/day, but not at 1,380 mg/kg/day (JBRC 1998a). Reduced body weight gain was also reported in female F344/DuCrj rats treated for 13 weeks with ≥870 mg 1,4-dioxane/kg/day and in male and female Crj:BDF_1 mice treated for the same duration with ≥1,830 mg/kg/day (JBRC 1998b). In the JBRC (1998a, 1998b) studies, reduction in weight gain was usually associated with reduced food consumption and/or reduced water consumption. Sherman rats treated with 1,015–1,599 mg 1,4-dioxane/kg/day for 2 years gained approximately 10% less weight throughout the study (estimated from graphic data in the paper) than controls or rats dosed with 94–148 mg/kg/day (Kociba et al. 1974). In the NCI (1978) bioassay, body weight of male rats in the high-dose group (530 mg/kg/day) and female mice (860 mg/kg/day) were lower than controls during the second year of the study. No data on food consumption were provided in these two chronic-duration studies. In another chronic study, treatment of male F344/DuCrj rats with up to 398 mg 1,4-dioxane/kg/day did not significantly affect body weight, but females dosed with 514 mg/kg/day gained 19% less weight than controls; the NOAEL in females was 103 mg/kg/day (JBRC 1998c). Neither food nor water consumption was significantly altered in this case. Male Crj:BDF_1 mice dosed with 768 mg 1,4-dioxane/kg/day for 2 years gained 43% less weight than controls, and females dosed with 323 and 1,066 mg/kg/day gained 15 and 45% less weight than controls, respectively (JBRC 1998c). The NOAELs for males and females were 251 and 77 mg/kg/day, respectively. In mice, the reductions in weight gain were accompanied by significant reductions in water consumption, but there were no significant changes in food consumption.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to 1,4-dioxane. No gross or histological alterations were observed in the lymph nodes, spleen, and thymus from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). No histopathologic alterations were observed in the spleen, thymus, and lymph nodes from rats dosed via drinking water with up to 1,599 mg 1,4-dioxane/kg/day for 2 years or from mice dosed similarly with up to 860 mg/kg/day (Kociba et al.

1974; NCI 1978). These NOAEL values for lymphoreticular effects are listed in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,4-dioxane. In an acute study in rabbits, a single gavage dose of 4,400 mg 1,4-dioxane/kg induced staggering in one of three rabbits and 6,600 mg/kg produced narcosis in one of three rabbits and was lethal to two other rabbits (Knoefel 1935). No further details were provided in this early study. Male and female F344/DuCrj rats dosed with 2,960 and 2,750 mg 1,4-dioxane/kg/day, respectively, for 2 weeks showed vacuolar changes in the brain (JBRC 1998a); the respective NOAELs were 1,010 and 1,040 mg/kg/day. Similar effects were reported in male and female F344/DuCrj rats dosed with 1,900 and 2,020 mg 1,4-dioxane/kg/day, respectively, for 13 weeks in the drinking water (JBRC 1998a); the respective NOAELs were 760 and 870 mg/kg/day. However, no significant alterations were seen in the spinal cord or sciatic nerve. In the same study, no histopathological alterations were observed in the brain, spinal cord, and sciatic nerve from Crj:BDF_1 mice dosed with up to 2,700 mg 1,4-dioxane/kg/day. No histopathologic alterations were observed in the brain, spinal cord, and sciatic nerve from rats dosed via the drinking water with up to 1,599 mg 1,4-dioxane/kg/day for 2 years or from mice dosed similarly with up to 860 mg/kg/day (JBRC 1998c; Kociba et al. 1974; NCI 1978). The NOAEL and LOAEL values for neurological effects are listed in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,4-dioxane.

Standard reproductive toxicity studies on 1,4-dioxane were not located. Only ancillary information is available. No gross or histological alterations were observed in the reproductive organs (testes, prostate, seminal vesicles, epididymis, uterus, ovaries, vagina) from rats and mice dosed with up to 2,020 and 2,700 mg 1,4-dioxane/kg/day, respectively, in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 514 and 1,066 mg 1,4-dioxane/kg/day, respectively, for 2 years (JBRC 1998c). No evidence of gross or microscopic alterations was found in the reproductive organs from rats exposed through the drinking water to up to 1,599 mg 1,4-dioxane/kg/day for up to 2 years (Kociba et al. 1974;

NCI 1978) or from mice exposed to up to 860 mg 1,4-dioxane/kg/day for up to 90 weeks (NCI 1978). These values are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to 1,4-dioxane. Only one relevant animal study was located. In that study, groups of pregnant Sprague-Dawley rats were administered 0, 258, 516, or 1033 mg 1,4-dioxane by gavage on gestation days 6–15 and sacrifices were conducted on gestation day 21 (Giavini et al.1985). Dams in the high-dose group gained less weight than controls and fetal weight in this group was reduced by 5.3% relative to controls. In addition, a slightly but significantly higher incidence of reduced sternum ossification was noticed in the high-dose group. No other significant differences between treated and control groups were observed, including number of implantations and of live fetuses, post-implantation loss, and incidence of malformations. The NOAEL and LOAEL values are presented in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding oral exposure of humans to 1,4-dioxane and cancer, but numerous studies have examined the carcinogenicity of 1,4-dioxane in animals exposed orally, in all of them the test material has been administered in the drinking water. In general, the studies in animals can be divided into a group in which numerous limitations are apparent, including small number of animals, low tumor incidences, lack of statistical analyses, and only one dose level was tested, and another small group of standard bioassays. To the former category belong Argus et al. (1965, 1973), Hoch-Ligeti and Argus (1970), and Hoch-Ligeti et al. (1970), whereas the standard bioassays include JBRC (1998c), Kociba et al. (1974), and NCI (1978).

Argus et al. (1965) exposed a group of 26 male Wistar rats to 1,4-dioxane in the drinking water at a concentration of 1% for 452 days. Nine rats served as controls. The maximal dose per rat was 132 g, which divided by an average exposure time of 452 days yields a daily dose of 584 mg/kg/day, assuming a reference body weight of 0.5 kg for mature male Wistar rats. End points examined included gross necropsy and histopathologic examination of tissues, but the range of tissues examined was not specified. Six of the 26 rats treated with 584 mg 1,4-dioxane/kg/day developed liver tumors that ranged in appearance from small neoplastic nodules to multifocal hepatocellular carcinomas. One treated rat had a

transitional cell carcinoma of the kidney and one rat that received a total dose of 116 g for 387 days (599 mg/kg/day) developed leukemia. One control rat developed a lymphosarcoma.

In a subsequent study by the same group of investigators, groups of male Sprague-Dawley rats (28–32/group) were treated with 1,4-dioxane in the drinking water for 13 months at levels of 0 (controls), 0.75, 1.0, 1.4, or 1.8% (Hoch-Ligeti et al. 1970). At termination, complete necropsy and histopathological examinations were conducted. Doses were estimated at about 400, 600, 800, and 1,000 mg/kg/day assuming that 13 months equals 390 days, a body weight of 0.6 kg for the rats, and the total dose provided in the study (104–256 g). Six treated rats developed tumors of the nasal cavity. All of the tumors consisted of squamous cell carcinomas with marked keratinization. The incidences were as follows: one at 0.75%, one at 1%, two at 1.4%, and two at 1.8%. Hepatocellular carcinomas were also observed in the rats that had nasal carcinomas in the 1.4 and 1.8% groups (Argus et al. 1973). In the latter study, in addition to incidences of hepatomas and hepatocellular carcinomas, the authors reported the incidences of "incipient" hepatomas. Two types of incipient hepatomas were observed, one consisting of large cells, apparently filled and distended with fat, and the other of finger-like strands of rather smaller hepatocytes with large hyperchromic nuclei and dense cytoplasm. According to Argus et al. (1973), these nodules showed all the histological characteristics of fully developed hepatomas. The following tumor incidences were reported: 4 incipient tumors at 0.75%, 9 incipient tumors at 1%, 13 incipient tumors and 3 hepatomas at 1.4%, and 11 incipient tumors and 12 hepatomas at 1.8% 1,4-dioxane. No tumors were found in the lungs. The authors stated that the effective tumor dose (TD5), the 50% tumor dose (TD50), and the maximum effective dose (TD95) were 72, 149, and 260 g, respectively, evaluated from the probit plot of the dose-response (Argus et al. 1973).

In the Kociba et al. (1974) study, groups of Sherman rats (60/sex/dose level) were treated with 1,4-dioxane in the drinking water at levels of 0 (controls), 0.01, 0.1, or 1% for 716 days. This corresponded to doses of 0, 9.6, 94, and 1,015 mg/kg/day in males and 0, 19, 148, and 1,599 mg/kg/day in females based on body weight and water consumption data. Treatment with 1,4-dioxane significantly increased mortality in high-dose males and females beginning at about 2–4 months of treatment. These rats showed degenerative changes in both the liver and kidneys. Body weight gain was significantly reduced in high-dose animals from the beginning of the study. Carcinogenic effects were limited to the liver and nasal turbinates. The investigators combined the incidence of tumors in males and females and expressed them as the effective incidences in the number of rats that were alive at 12 months. The incidence of all hepatic tumors was 2/106 (1.9%), 0/110 (0%), 1/106 (0.9%), and 12/66 (18.2%, p=00022) in controls, low-, mid-, and high-dose rats, respectively. The corresponding incidences of hepatocellular

carcinomas were 1/106 (0.9%), 0/110 (0%), 1/106 (0.9%), and 10/66 (15.2%, p=0.00033). Only three high-dose rats (one male and two females) had nasal carcinomas (p=0.05491) and were considered treatment-related by the investigators.

In the NCI (1978) bioassay, groups of Osborne-Mendel rats (35/sex/dose level) were administered 1,4-dioxane in the drinking water for 110 weeks. The estimated doses were 0 (controls), 240 and 530 mg/kg/day in males and 0, 350, and 640 mg/kg/day in males. Neoplasms associated with the administration of 1,4-dioxane occurred in the nasal cavity from males and females, liver from females, and testis/epididymis in males. The incidences of squamous cell carcinomas in the nasal turbinates were 0/33, 12/33 (36%), and 16/34 (47%) in control, low-, and high-dose males, respectively; the corresponding incidences in females were 0/34, 10/35 (29%), and 8/35 (23%). The first tumors were seen at week 52 in males and week 66 in females. Statistical analyses of these incidences revealed a significant dose-related trend and significant differences between treated groups and controls. The incidences of hepatocellular carcinomas in females were 0/31, 10/33 (30%), and 11/32 (34%) in controls, low-, and high-dose groups, respectively. A higher incidence of mesotheliomas of the vaginal tunics of the testis/epididymis was seen in treated males than in controls (2/33, 4/33, and 5/34 in controls, low-, and high-dose, respectively). The incidences of other neoplasms were not related to treatment with the test material by type, site, test group, or sex. Under the conditions of the study, 1,4-dioxane induced hepatocellular carcinomas in female rats and squamous cell carcinoma of the nasal turbinates in male and female rats.

In the JBRC (1998c) study, groups of Fischer 344/DuCrj rats (50/sex/dose level) received 1,4-dioxane in the drinking water at levels of 200, 1,000, and 5,000 ppm for 2 years (0, 16, 81, and 398 mg/kg/day for males; 0, 21, 103, and 514 mg/kg/day for females). Survival was significantly decreased in the high-dose groups due to liver and nasal tumors. Twenty-two of 50 high-dose male rats survived compared to 40/50 in controls; 24/50 of high-dose females survived compared to 38/50 in controls. In high-dose males (398 mg/kg/day), the incidence of nasal cavity tumors was 7/50 ($p<0.01$) compared to none in the other groups; in high-dose females (514 mg/kg/day), the incidence was 8/50 ($p<0.01$) compared to none in the other groups. The nasal tumors included squamous cell carcinomas, sarcomas, rhabdomyosarcoma, and esthesioneuroepithelioma. The incidence of combined hepatocellular adenoma or carcinoma in males was 0/50, 2/50, 4/49, and 33/50 ($p<0.01$) in the control, low-, mid-, and high-dose male rats; the corresponding incidences in females were 1/50, 0/50, 5/50, and 40/50 ($p<0.01$). High-dose males also had an increased incidence of mesothelioma of the peritoneum (28/50 compared to 2/50 in controls).

High-dose females had an increased incidence of mammary gland adenomas (16/50 compared to 6/50 in controls).

Two studies have been conducted in mice. Groups of B6C3F$_1$ mice (50/sex/dose level) were administered 1,4-dioxane in the drinking water for 90 weeks (NCI 1978). Based on body weight and water consumption data, the investigators estimated that the water provided doses of 0 (controls), 720, and 830 mg/kg/day in males, and 0, 380, and 860 mg/kg/day in females. Mortality was significantly increased (dose-related) in female mice. In female mice, 28/50, (56%) in the high-dose group, 39/50 (78%) in the mid-dose group, and 45/50 (90%) in the control group were still alive on week 91 of the study. In males, at least 90% of the mice in each group were still alive at week 91. Treatment with 1,4-dioxane significantly increased the incidence of liver tumors. The incidences of hepatocellular carcinoma were 2/49 (4%), 18/50 (36%), and 24/47 (51%), in controls, low-, and high-dose males, respectively; the corresponding incidences in females were 0/50, 12/48 (25%), and 29/37 (78%). The incidences of hepatocellular carcinomas or adenomas in males were 8/49 (16%), 19/50 (38%), and 28/47 (60%); the incidences in females were 0/50, 21/48 (44%), and 35/37 (95%). The incidences of these tumors were statistically significant for dose-related trend and for direct comparisons with controls. No other neoplasm, benign, or malignant, was found to be associated to treatment with 1,4-dioxane.

In another study (JBRC 1998c), groups of Crj:BDF$_1$ mice (50/sex/dose level) received 1,4-dioxane in the drinking water at levels of 500, 2,000, and 8,000 ppm for 2 years (0, 66, 251, and 768 mg/kg/day for males; 0, 77, 323, and 1,066 mg/kg/day for females). Early mortality occurred in female mice, and this was attributed to liver tumors. Survival rates at 104 weeks in females were 29/50, 29/50/ 17/50, and 5/50 in control, low-, mid-, and high-dose groups, respectively. A significant and dose-related increase in the incidence of liver adenomas and carcinomas of the liver was found in female mice. The incidences of combined adenomas and carcinomas in control, low-, mid-, and high-dose females were 4/50, 34/50, 41/40, and 46/50 ($p<0.01$ for all treated groups). High-dose males (768 mg/kg/day) also showed a significant increased incidence of hepatocellular carcinomas; the combined incidences of adenomas and carcinomas, as the dose increased, were 21/50 (controls), 31/50, 37/50, and 39/50 ($p<0.01$). There were no nasal cavity tumors in male or female mice.

In the single study in guinea pigs, a group of 22 male guinea pigs was administered 1,4-dioxane in the drinking water at concentrations of 0.5–2% for 23 months (Hoch-Ligeti and Argus 1970). Ten guinea pigs served as controls. The investigators stated that the total intake of 1,4-dioxane during the 23 months of the experiment was 588–625 g. Assuming a reference body weight of 0.84 kg and converting

23 months into 690 days (30 days/month), the intake of 1,4-dioxane was approximately 1,014–1075 mg/kg/day. All of the animals were sacrificed within 28 months. Very little additional data were presented in this brief note. Examination of the lungs revealed peri- or intrabronchial epithelial hyperplasia and nodular mononuclear infiltration in nine of the treated guinea pigs. In addition, two guinea pigs had carcinoma of the gall bladder, three had early hepatomas, and one had adenoma of the kidney. No tumors were found in the controls.

1,4-Dioxane was tested also as a cancer initiator in mice (Bull et al. 1986) and promoter in rats (Lundberg et al. 1987). Female Sencar mice were dosed with 1,000 mg 1,4-dioxane/kg by gavage before receiving topical applications of 1 μg of 12-O-tetradecanoylphorbol-13-acetate (TPA) 3 times/week for 20 weeks. A control group was initiated with acetone before the TPA application. Administration of 1,4-dioxane did not increase the formation of papillomas compared to mice initiated with acetone and promoted with TPA, indicating a lack of initiating activity under the conditions of the study. The tumor promotion activity of 1,4-dioxane was studied in groups of male Sprague-Dawley rats (8–11/group). All rats went through a 2/3 hepatectomy before receiving a single intraperitoneal injection of 30 mg/kg of diethylnitrosamine (DENA). Five days later, treatment with 100 or 1,000 mg/kg of 1,4-dioxane by gavage in saline started once daily, 5 days/week for 7 weeks. One week after the last treatment, the rats were killed, the liver was removed and stained for gamma-glutamyl-transpeptidase (GGT), and the number and total volume of GGT-positive foci was studied. 1,4-Dioxane alone had no significant effect on the end points evaluated. In DENA initiated rats, the high-dose of 1,4-dioxane induced a significant increase in the number of foci and total volume of foci relative to rats treated with DENA alone. The livers of high-dose rats showed enlarged foamy hepatocytes mainly in midzonal regions. The foamy appearance was due to vacuoles shown to contain fat. The results indicated promotion activity by 1,4-dioxane.

The data available indicate that 1,4-dioxane produced liver and nasal cancer in rats and liver tumors in mice. The EPA has derived an oral cancer potency factor of 0.011 $(mg/kg/day)^{-1}$ for 1,4-dioxane using the Linearized Multistage Model (IRIS 2004). This factor was calculated from oral exposure data reported by NCI (1978) regarding incidence of tumors of the nasal turbinates in male Osborne-Mendel rats. The lifetime average doses that would result in risk of $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, and $1x10^{-7}$ are $9x10^{-3}$, $9x10^{-4}$, $9x10^{-5}$, and $9x10^{-6}$ mg/kg/day, respectively, as indicated in Figure 3-2. The EPA is currently re-evaluating the health assessment for 1,4-dioxane (EPA 2004f).

3.2.3 Dermal Exposure

3.2.3.1 Death

As mentioned in Section 3.2.1.1, Johnstone (1959) described a fatal case of a worker exposed to 1,4-dioxane for only 1 week and whose post-mortem examination showed kidney and liver alterations. The room in which the patient had worked had no exhaust ventilation and the worker was not provided a respirator. Dermal exposure in this case may have been considerable since the worker used liquid 1,4-dioxane to keep his hands free of glue. A dermal LD_{50} of 7,600 mL/kg was reported for rabbits (RTECS 2004); this value is presented in Table 3-3.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, or body weight effects in humans or in animals after dermal exposure to 1,4-dioxane. No studies were located regarding hepatic and renal effects in humans following dermal exposure to 1,4-dioxane.

The highest NOAEL and all reliable LOAEL values from each study for systemic effects in each species and duration category are recorded in Table 3-3.

Hepatic Effects. In a study with four guinea pigs, approximately 143 mg 1,4-dioxane/kg was applied to a clipped area of the nape 5 days/week for 49–101 days (Fairley et al. 1934). Upon sacrifice on days 49, 66, 77, and 101, no gross alterations of the liver were observed, but there were indications of patchy cell degeneration. The same protocol conducted in four rabbits applied doses of approximately 57 mg/kg showed vascular congestion of the liver and patchy cell degeneration in two of the rabbits (Fairley et al. 1934).

Renal Effects. Application of approximately 143 mg 1,4-dioxane/kg to a clipped area of the nape of guinea pigs 5 days/week for 49–101 days resulted in renal cortical cell degeneration and hemorrhages. The same experiment conducted in rabbits applied approximately 57 mg 1,4-dioxane/kg resulted in the same type of kidney lesions (Fairley et al. 1934).

Table 3-3 Levels of Significant Exposure to 1,4-Dioxane - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL					Reference Chemical Form
				Less Serious			Serious		
ACUTE EXPOSURE									
Death									
Rabbit (NS)	once					7600 ml/kg	(LD50)		RTECS 2004
Systemic									
Human	3 min	Ocular	2000 ppm						Fairley et al. 1934
Human	15 min	Ocular	200 B ppm	300 B ppm	(eye irritation)				Silverman et al. 1946
Human	10 min	Ocular		1600 ppm	(slight eye irritation)				Yant et al. 1930
Human	6 hr	Ocular		50 M ppm	(eye irritation)				Young et al. 1977
Rat (Wistar)	once	Dermal	8300 M mg/kg						Clark et al. 1984

Table 3-3 Levels of Significant Exposure to 1,4-Dioxane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE						
Systemic						
Gn Pig (NS)	49-101 d 5 d/wk 2 x/d	Hepatic			143 mg/kg (cloudy swelling and patchy cell degeneration)	Fairley et al. 1934
		Renal			143 mg/kg (degeneration and necrosis of cortical tubules)	
		Dermal	143 mg/kg			
Rabbit (NS)	49-101 d 5 d/wk 2 x/d	Hepatic			57 mg/kg (patchy cell degeneration)	Fairley et al. 1934
		Renal			57 mg/kg (tubular cell degeneration)	
		Dermal	57 mg/kg			

d = day(s); Gn pig = guinea pig; hr - hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; ml/kg = milliliter per kilogram; mg/kg = milligram per kilogram; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million; wk = week(s); x = time(s)

Dermal Effects. Application of a single dose of up to 8,300 mg 1,4-dioxane/kg to an uncovered area of the skin of rats produced no signs of skin irritation within the period of observation of 14 days (Clark et al. 1984). Application of approximately 143 mg 1,4-dioxane/kg 5 days/week for 40–101 days to a clipped area of the nape from guinea pigs did not produce skin irritation (Fairley et al. 1934). Similar results were obtained in rabbits applied approximately 57 mg 1,4-dioxane/kg using the same protocol (Fairley et al. 1934).

Ocular Effects. The ocular effects observed in humans and in animals described in Section 3.2.1.2 and listed in Table 3-1 are assumed to have occurred by direct contact of vapors of 1,4-dioxane with eyes and are also listed in Table 3-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,4-dioxane:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

The carcinogenicity and initiator and promoter properties of 1,4-dioxane have been evaluated. To test whether 1,4-dioxane is a complete carcinogen, 0.2 mL of a solution of 1,4-dioxane (unspecified concentration) were applied to the shaved back from Swiss-Webster mice for 60 weeks (King et al. 1973). Examination of the skin at week 60 revealed only one skin sarcoma and one lymphoma, suggesting that under the conditions of the study, 1,4-dioxane was not a complete carcinogen. King et al. (1973) also tested whether 1,4-dioxane is a promoter by applying 15 μg of dimethylbenzanthracene (DMBA) to groups of Swiss-Webster followed 1 week later by the application of 0.2 mL of a solution of 1,4-dioxane (unspecified concentration) to the shaved back for 60 weeks. At week 60, only 4 males and 5 females were still alive (out of 30/sex). Treatment with 1,4-dioxane in mice initiated with DMBA resulted in an increased number of tumors in the skin, lungs, and kidneys. The activity of 1,4-dioxane in promoting skin tumors was similar to that observed with croton oil as a promoter. However, croton oil led to a much higher multiplicity of skin tumors per mouse than 1,4-dioxane. Bull et al. (1986) tested 1,4-dioxane as an

initiator. In that study, female Sencar mice were applied topical doses of 1,000 mg 1,4-dioxane/kg before receiving topical applications of 1 μg 12-O-tetradecanoylphorbol-13-acetate (TPA) 3 times/week for 20 weeks. A control group received an application of acetone before the TPA application. 1,4-Dioxane did not increase the formation of papillomas compared to mice initiated with acetone and promoted with TPA.

3.3 GENOTOXICITY

Studies of the *in vitro* and *in vivo* genotoxicity of 1,4-dioxane are summarized in Tables 3-4 and 3-5, respectively. 1,4-Dioxane was not genotoxic in standard *in vitro* tests of gene mutation in bacteria in the presence or absence of metabolic activation (Haworth et al. 1983; Khudoley et al. 1987; Morita and Hayashi 1998; Nestmann et al. 1984; Stott et al. 1981). Kwan et al. (1990) tested 1,4-dioxane in a strain of *Photobacterium phosphoreum*, which is sensitive to chemicals that are DNA-damaging agents, DNA-intercalating agents, DNA-synthesis inhibitors, and direct mutagens. 1,4-Dioxane showed no activity in the absence of metabolic activation, but was not tested with metabolic activation. No evidence of DNA damage was seen in *Escherichia coli* K-12 *uvrB/recA* incubated with 1,4-dioxane with or without metabolic activation (Helmér and Bolcsfoldi 1992). A study in the yeast *Saccharomyces cerevisiae* strain D61M also gave negative results for chromosomal aneuploidy without activation (Zimmermann et al. 1985), but was not repeated in the presence of metabolic activation. Studies with isolated mammalian cells exposed to 1,4-dioxane have also yielded negative results. For example, assays for induction of micronuclei, sister chromatid exchanges, and chromosomal aberrations in Chinese hamster ovary cells (CHO) were negative with and without metabolic activation (Morita and Hayashi 1998). A similar study by Galloway et al. (1987) also found no increase in chromosomal aberrations in CHO cells but did observe a slight increase in the incidence of sister chromatid exchanges in the absence of activation. Morita and Hayashi (1998) and McGregor et al. (1991) found no increase in gene mutations in mouse lymphoma cells incubated with 1,4-dioxane. 1,4-Dioxane did not induce DNA damage in rat hepatocytes (Goldsworthy et al. 1991), but increased cell transformations in BALB/3t3 cells at cytotoxic concentrations (Sheu et al. 1988). A test for DNA single strand breaks in rat hepatocytes incubated with 1,4-dioxane yielded positive results only at cytotoxic concentrations of 1,4-dioxane (Sina et al. 1983).

Studies of *in vivo* exposure of organisms to 1,4-dioxane also have been mostly negative, although some positive results have been reported. The only information in humans is that no increases in chromosomal

Table 3-4. Genotoxicity of 1,4-Dioxane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Salmonella typhimurium (TA100, TA98, TA1535, TA1537)	Gene mutation	–	–	Haworth et al. 1983
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Stott et al. 1981
S. typhimurium (TA100, TA1535)	Gene mutation	–	–	Nestmann et al. 1984
S. typhimurium (TA98, TA100, TA1530, TA1535, TA1537)	Gene mutation	–	–	Khudoley et al. 1987
Photobacterium phosphoreum	DNA damage	NT	–	Kwan et al. 1990
Escherichia coli K-12 *uvrB*/*recA*	DNA damage	–	–	Hellmer and Bolcsfoldi 1992
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Morita and Hayashi 1998
E. coli (WP2, WP2 *uvrA*)	Gene mutation	–	–	Morita and Hayashi 1998
Saccharomyces cerevisiae (D61M)	Chromosomal malsegregation	NT	–	Zimmermann et al. 1985
Mouse lymphoma cells	Gene mutation	–	–	Morita and Hayashi 1998
CHO-K1 cells	Chromosomal aberrations	–	–	Morita and Hayashi 1998
CHO-K1 cells	Sister chromatid exchange	–	–	Morita and Hayashi 1998
CHO-K1 cells	Micronuclei	–	–	Morita and Hayashi 1998
Rat hepatocytes	DNA repair	–	–	Goldsworthy et al. 1991
CHO-W-B1 cells	Chromosomal aberrations	–	–	Galloway et al. 1987
CHO-W-B1 cells	Sister chromatid exchange	–	±	Galloway et al. 1987
Mouse lymphoma cells	Gene mutation	–	–	McGregor et al. 1991
BALB/3T3 cells	Cell transformation	NT	+	Sheu et al. 1988

– = negative result; + = positive result; ± = weak positive result; CHO = Chinese hamster ovary; NT = not tested

Table 3-5. Genotoxicity of 1,4-Dioxane *In Vivo*

Species (test system)	End point	Results	Reference
Human peripheral lymphocytes	Chromosomal aberrations	–	Thiess et al. 1976
Rat hepatocytes	DNA repair	–	Goldsworthy et al. 1991
Rat nasal epithelial cells	DNA repair	–	Goldsworthy et al. 1991
Mouse hepatocytes	Micronuclei	+	Morita and Hayashi 1998
Mouse peripheral blood	Micronuclei	–	Morita and Hayashi 1998
Rat hepatocytes	DNA alkylation or repair	–	Stott et al. 1981
Rat hepatocytes	DNA damage	+	Kitchin and Brown 1990, 1994
Mouse bone marrow	Micronuclei	–	Tinwell and Ashby 1994
Mouse bone marrow (C57BL6)	Micronuclei	+	Mirkova 1994
Mouse bone marrow (BALB/c)	Micronuclei	–	Mirkova 1994
Mouse bone marrow	Micronuclei	–	McFee et al. 1994
Drosophila (food)	Dominant lethal	–	Yoon et al. 1985
Drosophila (food)	Meiotic non-disjunction	+	Muñoz and Barnett 2002

– = negative result; + = positive result; ± = weak positive result

aberrations were observed in peripheral lymphocytes from a groups of six workers employed in 1,4-dioxane production relative to observations made in six control subjects (Thiess et al. 1976). Several studies have reported results regarding micronuclei formation. An assay in bone marrow cells from C57BL6 mice after single gavage doses of up to 3,600 mg 1,4-dioxane/kg found a dose-related increase in the incidence of micronuclei, but the results in BALB/c mice were negative (Mirkova 1994). A similar study by Tinwell and Ashby (1994) found that 1,4-dioxane did not induce micronuclei in bone marrow cells from CBA mice treated with a single oral dose of 1,800 mg/kg or from C57BL6 mice dosed with 3,600 mg/kg. Studies reported by McFee et al. (1994) of several trials conducted by two different laboratories yielded equivocal results for micronuclei formation in mouse bone marrow. More recent data by Morita and Hayashi (1998) in CD-1 mice treated with a single gavage dose of up to 3,000 mg 1,4-dioxane/kg showed an increase in micronuclei in hepatocytes, but not in peripheral blood reticulocytes. Hepatocytes from Sprague-Dawley rats dosed with a single dose of 1,000 mg 1,4-dioxane/kg by gavage showed no evidence of DNA alkylation or DNA repair activity (Stott et al. 1981). This dose level administered via the drinking water to the rats for 11 weeks induced minimal hepatocellular swelling, which was accompanied by increased DNA synthesis (Stott et al. 1981). In male Fischer 344 rats administered single doses of up to 2,000 mg 1,4-dioxane/kg by gavage, 1,4-dioxane did not induce replicative DNA synthesis in hepatocytes (Uno et al. 1994), but it did in a subsequent study by the same group of investigators (Miyagawa et al. 1999). In liver tissue from Sprague-Dawley rats given two doses of 2,550 or 4,200 mg 1,4-dioxane/kg, there was a dose-related increase in DNA damage (assessed by alkaline elution) and cytochrome P-450 content; no significant effect was seen at ≤840 mg/kg (Kitchin and Brown 1990). Administration of a single oral dose of 1,000 mg 1,4-dioxane/kg to Fischer 344 rats produced no evidence of hepatocyte DNA repair, and the same negative response was obtained in rats dosed for a week via drinking water containing up to 2% 1,4-dioxane (Goldsworthy et al. 1991). No DNA repair activity was also observed in nasal epithelial cells from rats given 1% 1,4-dioxane in the drinking water for 8 days followed by a single gavage dose of 1,000 mg/kg (Goldsworthy et al. 1991). 1,4-Dioxane did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* in one study (Yoon et al. 1985), but was positive for meiotic non-disjunction in another study in *D. melanogaster* (Muñoz and Barnett 2002).

Collectively, the information available suggests that 1,4-dioxane is a non-genotoxic compound, or at best, a weakly genotoxic compound.

3.4 TOXICOKINETICS

The absorption of 1,4-dioxane following oral or inhalation exposure is rapid and virtually complete. Absorption after dermal exposure appears to be much less extensive. 1,4-Dioxane is widely distributed and rapidly metabolized in both humans and animals either to β-hydroxyethoxyacetic acid (HEAA) or to its interconversion product, 1,4-dioxane-2-one, which can form under acid conditions. Both forms are rapidly and extensively eliminated in the urine. Metabolism to HEAA or 1,4-dioxane-2-one in rats is dose-dependent, becoming saturated at high doses. Unchanged 1,4-dioxane is excreted in the urine and the expired air, mainly at high dose levels. 1,4-Dioxane and its major metabolite show little tendency to accumulate in the body.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Young et al. (1977) exposed a group of four healthy male volunteers to 50 ppm of 1,4-dioxane vapor by inhalation for 6 hours. Plasma concentrations of 1,4-dioxane climbed rapidly during the first 2 hours of exposure, and more slowly thereafter, indicating an initial rapid absorption, followed by a plateau phase in which steady-state levels in plasma were being approached or had been reached. Based on the presence of 1,4-dioxane and its main metabolite (HEAA) in the urine, the calculated total absorbed dose of 1,4-dioxane was 5.4 mg/kg, and the calculated rate was 76.1 mg/hour.

In rats exposed by head-only inhalation to 50 ppm of 1,4-dioxane for 6 hours, a total absorbed dose of 71.9 mg/kg was estimated, based on the detection of the compound and its primary metabolite (HEAA) in the urine (Young et al. 1978a, 1978b). The concentration of 1,4-dioxane in the plasma was 7.3 µg/mL at the end of exposure. It is of note that the value for total absorbed dose in this study, on a per body weight basis, is considerably greater than that calculated from volunteers exposed to the same airborne concentration of 1,4-dioxane for the same length of time (Young et al. 1977).

3.4.1.2 Oral Exposure

Data on the absorption of 1,4-dioxane following oral exposure in humans are not available.

Young et al. (1978a, 1978b) exposed groups of male Sprague-Dawley rats to 10, 100, or 1,000 mg/kg of uniformly labeled ^{14}C-1,4-dioxane by gavage, and reported that <2% of the label was found in the feces in the first 24 hours (10 mg/kg dose) or 72 hours (100 or 1,000 mg/kg doses), indicating rapid and nearly-complete absorption of the compound from the gastrointestinal tract. In another experiment in the same manuscript (Young et al. 1978a, 1978b), groups of male Sprague-Dawley rats were exposed to 10, 100, or 1,000 mg/kg of uniformly labeled ^{14}C-1,4-dioxane by gavage daily for 17 days. Less than 2% of the total administered label was recovered in the feces in 480 hours post-exposure, indicating that at least 98% absorption had occurred.

3.4.1.3 Dermal Exposure

Data on the absorption of 1,4-dioxane in humans following dermal exposure are not available, but a lethal case of intoxication with 1,4-dioxane in which the patient had extensive dermal contact with 1,4-dioxane in addition to inhalation of vapors suggests that dermal absorption is possible (Johnstone 1959).

Marzulli et al. (1981) applied uniformly labeled ^{14}C-1,4-dioxane, dissolved in either methanol or skin lotion, to the unoccluded skin of Rhesus monkeys and measured the ability of the compound to penetrate the skin by analysis of radiolabel in the urine. The skin penetration of 1,4-dioxane was minimal, being <4% in all cases; however, because the skin was unoccluded, evaporation may have influenced the study results.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Data on the distribution of 1,4-dioxane following inhalation exposure in humans or animals are not available.

3.4.2.2 Oral Exposure

Data on the distribution of 1,4-dioxane following oral exposure in humans or animals are not available.

3.4.2.3 Dermal Exposure

Data on the distribution of 1,4-dioxane following dermal exposure in humans or animals are not available.

3.4.2.4 Other Routes of Exposure

The distribution of ^{3}H-1,4-dioxane was determined in male Sprague-Dawley rats after intraperitoneal injection of 6.97 mg/kg (Woo et al. 1977b). Levels of activity were measured in whole blood, liver, kidney, spleen, lung, colon, and skeletal muscle at 1, 2, 6, and 16 hours. The radioactivity was widely distributed, with concentrations of dioxane equivalents at 1 and 16 hours decreasing from 93.4 to 41.4 nmol/mL in the blood, from 59.1 to 24.2 nmol/g in the liver, from 116.1 to 31.9 nmol/g in the kidney, from 49.6 to 30 nmol/g in the spleen, from 52.2 to 23.2 nmol/g in the lung, from 56.1 to 27.7 nmol/g in the colon, and from 45.3 to 28.1 nmol/g in skeletal muscle. It should be noted that the tissue samples were not perfused or corrected for levels of blood in the tissue, so there might have been some influence of the blood-borne activity on the reported tissue values. Within the tissues, the percent covalent binding at 16 hours was universally <20%, with the highest levels in the colon (17.3% bound), spleen (16.4% bound), and liver (13.7% bound), followed by the lung (11.2% bound), kidney (9.5% bound), whole blood (3.1% bound), and skeletal muscle (2.7% bound). Within the cells, the highest activity levels were found in the cytosol (~68% at 6 hours post-exposure), with lesser amounts in the microsomal (~15% at 6 hours post-exposure), mitochondrial (~14% at 6 hours post-exposure), and nuclear (<3% at 6 hours post-exposure) fractions. Interestingly, percent covalent binding was entirely opposite in proportion to total activity levels, with the greatest percent binding found in the nuclear fraction (~65%), followed by the mitochondrial (~46%), microsomal (~34%), and cytosolic (~5%) fractions.

Mikheev et al. (1990) exposed rats to ^{14}C-1,4-dioxane by intraperitoneal injection, and evaluated the levels of radioactivity in the blood, brain, testes, liver, and kidney at 5, 15, and 30 minutes and at 1, 3, and 6 hours post-injection in order to determine the tissue:blood concentration ratios. For all evaluated tissues at all time points, the tissue:blood ratio was between 0.5 and 1.5, indicating that 1,4-dioxane is distributed evenly and does not appreciably accumulate in any of the evaluated tissues. The maximum accumulation time (Tmax) was 5 minutes for liver and kidney, and 15 minutes for the blood, brain, and testes.

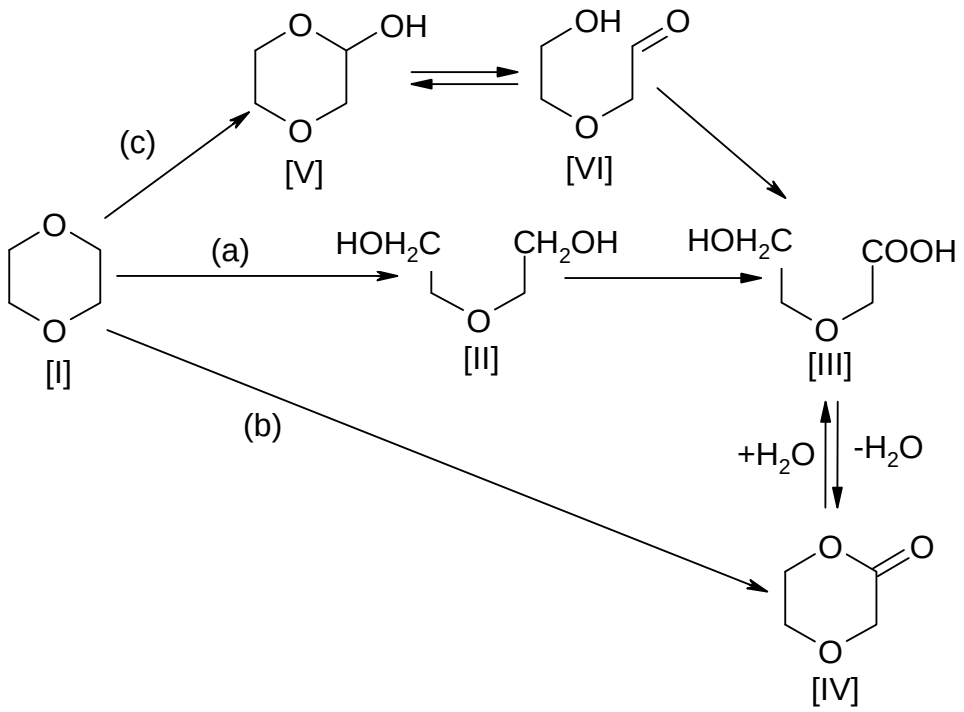
3.4.3 Metabolism

A proposed metabolism scheme for 1,4-dioxane is diagrammed in Figure 3-3.

The exact metabolic pathways of 1,4-dioxane metabolism are not known. However, numerous studies have reported that 1,4-dioxane is metabolized to a single urinary metabolite, believed to be HEAA. There is some question as to whether HEAA or 1,4-dioxane-2-one is the ultimate metabolite (Braun and Young 1977; Woo et al. 1977a, 1977b, 1977c; Young et al. 1977). This arises from the fact that under acid conditions, such as are often used in analytical assays, HEAA can be converted to 1,4-dioxane-2-one, and under alkaline conditions, the reverse reaction occurs. It is of note that HEAA is not volatile, and as a result, is often catalyzed to 1,4-dioxane-2-one in order to facilitate analysis, which may explain why Woo et al. (1977a, 1977d) reported 1,4-dioxane-2-one, rather than HEAA. As mentioned above, acid conditions, such as were employed by the assays of Woo et al. (1977a, 1977d) result in the formation of 1,4-dioxane-2-one from HEAA. Additional evidence for HEAA as the primary metabolite, rather than 1,4-dioxane-2-one, comes from a structure-activity relationship analyses of the genotoxicity of the two putative 1,4-dioxane metabolites (Blake 1995; Gombar 1995). 1,4-Dioxane-2-one is predicted to be strongly mutagenic, based on its structure, while HEAA would be only weakly genotoxic; the observed results of tests of genotoxicity for 1,4-dioxane correlate much closer with the predicted results from HEAA than from those of 1,4-dioxane-2-one. However, given the fact that the analytical methods used for analysis of the metabolites of 1,4-dioxane are capable of causing the formation of 1,4-dioxane-2-one from HEAA, and the reverse reaction as well, there is still some uncertainty as to the actual identity of the metabolite that has not been resolved.

Mixed-function oxidase enzymes, and cytochrome P-450 in particular, are critical to the metabolism of 1,4-dioxane, as induction of these enzymes increases the rate of HEAA formation, and inhibition decreases HEAA formation (Woo et al. 1977c, 1978). The initial step in metabolism is likely a P-450-catalyzed oxidative step; however the specific oxidation that occurs has not yet been determined.

Figure 3-3. Suggested Metabolic Pathways of 1,4-Dioxane in the Rat*



I = 1,4-dioxane; II = diethylene glycol; III = β-hydroxyethoxy acetic acid (HEAA); IV = 1,4-dioxane-2-one; V = 1,4-dioxane-2-ol; VI = β-hydroxyethoxy acetaldehyde

*Adapted from Woo et al. (1977c)

One possibility is diagrammed in pathway (a) of Figure 3-3. Cytochrome P-450 could act on one of the oxane oxygens, resulting in a decyclization and the formation of diethylene glycol. Evidence supporting this pathway comes from the fact that in animals injected with diethylene glycol, HEAA was found as the major metabolite (Woo et al. 1977a). Diethylene glycol could then be further metabolized to HEAA through an additional oxidative metabolic step. Alternately, cytochrome P-450 enzymes could act on one of the carbons in 1,4-dioxane to add a single oxygen atom, resulting in the direct formation of 1,4-dioxane-2-one as diagrammed in pathway (b) of Figure 3-3; however, no evidence is presently available to support this possible pathway. Another possibility is that rather than a single oxygen, a hydroxyl group could be added to a carbon atom, resulting in 1,4-dioxane-2-ol, as shown in pathway (c) of Figure 3-3. Additional oxidation to HEAA, resulting in a breaking of the ring structure, and further hydrolysis to HEAA could follow. As with pathway (b), there is no direct evidence supporting pathway (c) as the pathway for 1,4-dioxane metabolism.

1,4-Dioxane is extensively metabolized to HEAA in humans. Young et al. (1977) reported that over 99% of the urinary elimination of 1,4-dioxane after a 4-hour exposure of volunteers to 50 ppm occurred as HEAA rather than the parent compound. In a later study, the ratio of HEAA to dioxane in the urine of humans following a 7.5-hour exposure to 1.6 ppm dioxane was 118:1, indicating nearly complete metabolism at this exposure concentration.

The metabolism of 1,4-dioxane to HEAA in animals is nearly complete, as evidenced by studies examining the urine of exposed animals. Following inhalation exposure of rats to 50 ppm of 1,4-dioxane for 6 hours, the ratio of HEAA to dioxane in the urine over the 48-hour observation period was >3,000, indicating that for urinary elimination, nearly all of the compound was eliminated as the metabolite, rather than as the parent compound (Young et al. 1978a, 1978b).

The available animal data indicate that the metabolism of 1,4-dioxane is saturable. Young et al. (1978a, 1978b) reported that with an increasing oral dose level, a greater percentage of the total dose was eliminated as expired 1,4-dioxane, suggesting that the normally-rapid metabolism of 1,4-dioxane had reached a maximum, allowing the free compound to circulate in the blood and be eliminated by respiration; no dose-related differences were seen in elimination as CO_2 or in the feces that could otherwise account for this difference. A similar pattern was seen following 17 repeated doses of 10 or 1,000 mg/kg of ^{14}C-1,4-dioxane, with a greater elimination of label, primarily as the metabolite, in the urine at the lower dose, with the higher dose resulting in a greater elimination, as both ^{14}C-1,4-dioxane

and $^{14}CO_2$, in the expired air (Young et al. 1978a, 1978b). In an intravenous study reported in the same manuscript, the metabolic clearance of 1,4-dioxane decreased from 2.82 mL/minute following a single injection of 10 mg/kg to 0.17 mL/minute following an injection of 1,000 mg/kg, indicating that the metabolic capacity to metabolize 1,4-dioxane to HEAA had been saturated.

Woo et al. (1977a) reported that in the urine of rats orally exposed to 1–4 g/kg, only one metabolite was detected by gas chromatography. This metabolite was identified as 1,4-dioxane-2-one using nuclear magnetic resonance (NMR), infrared, and gas chromatograph-mass spectroscopy. Administration of diethylene glycol to rats resulted in the formation of the same metabolite, leading the study authors to hypothesize that diethylene glycol may represent an intermediate metabolite in the formation of 1,4-dioxane-2-one. In a later study by the same authors (Woo et al. 1977b), urine samples were collected, with glacial acetic acid as a preservative, from rats for 2 days following intraperitoneal injection of 50–400 mg/kg 1,4-dioxane. Gas chromatography identified a single metabolite, which was confirmed to be 1,4-dioxane-2-one by NMR, infrared, and mass spectroscopy.

Braun and Young et al. (1977) exposed groups of rats to radiolabeled 1,4-dioxane and characterized the major radiolabeled metabolite in the urine. The metabolite behaved identically to standards of both HEAA and 1,4-dioxane-2-one when evaluated using gas chromatography coupled with mass spectroscopy, preventing determination of the identity of the metabolite by this method. Using thin-layer chromatography, the metabolite's R_f value (the ratio of spot distance traveled to distance of the solvent front) of 0.60 correlated with that of HEAA (0.61) rather than that of 1,4-dioxane-2-one (1.00). The study authors therefore concluded that the identity of the urinary metabolite in rats was HEAA, rather than 1,4-dioxane-2-one, but noted the tendency for HEAA to cyclize under acidic conditions, forming 1,4-dioxane-2-one.

Woo et al. (1977c, 1978) pretreated groups of rats with phenobarbital (PB), Arochlor 1254 mixture (PCB), or 3-methylcholanthrene (MC) and examined the effects on the metabolism of an intraperitoneal dose of 1,4-dioxane. Pretreatment with PB resulted in a much more rapid metabolism of 1,4-dioxane, with the majority of the dose eliminated in the urine as HEAA within 32 hours, compared to 40 hours for the controls. The addition of 2,4-dichloro-6-phenylphenoxy ethylamine (DPEA), a cytochrome P-450 inhibitor, resulted in a reversal of this effect. Pretreatment with PCB resulted in similar effects as PB, while pretreatment with MC had no effect. Pretreatment with cobaltous chloride, to suppress P-450 synthesis, resulted in a decreased metabolite elimination, further implicating cytochrome P-450 enzymes in the metabolism of 1,4-dioxane.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

1,4-Dioxane and its metabolite, HEAA, were found in the urine of workers exposed to a time-weighted average concentration of 1.6 ppm of 1,4-dioxane for 7.5 hours (Young et al. 1976). The concentration of HEAA was 414 µmol/L, and that of unchanged 1,4-dioxane was only 3.5 µmol/L suggesting rapid and extensive metabolism. In four volunteers exposed to 50 ppm of 1,4-dioxane for 6 hours, over 99% of the urinary elimination of the compound occurred as its metabolite HEAA (Young et al. 1977) during the exposure period or within the 18 hours post-exposure; the remainder of the urinary elimination occurred as the parent compound. The half-life of elimination of 1,4-dioxane from plasma was 59 minutes, of dioxane in urine was 48 minutes, and of HEAA in the urine was 2.7 hours. The urinary elimination data suggested that elimination kinetics of 1,4-dioxane and HEAA are best described with first-order, one-compartment kinetic models. Elimination by other pathways (e.g., feces, expired air) was not evaluated in this study.

Following inhalation exposure in animals, the primary route of elimination is believed to be the urine. Young et al. (1978a, 1978b) reported that following inhalation exposure in rats, urinary elimination of 1,4-dioxane was primarily as HEAA, rather than as the parent compound.

3.4.4.2 Oral Exposure

Data on the elimination of 1,4-dioxane in humans following oral exposure are not available.

The administered dose of 1,4-dioxane has an effect on elimination of the compound. While urinary elimination is the predominant pathway regardless of dose, at large doses, elimination in the expired air plays a greater role, possibly due to the saturable pathways of 1,4-dioxane metabolism. After single oral doses of ^{14}C-1,4-dioxane in rats, 99% of the label was recovered in the urine and <1% was recovered in the expired air at 10 mg/kg; 86% of the label was recovered in the urine and 4.7% in the expired air at 100 mg/kg; and 76% of the label was found in the urine and 25% in the expired air at 1,000 mg/kg (Young et al. 1978a, 1978b). Similar results were seen following 17 daily gavage doses of ^{14}C-1,4-dioxane in rats, with 99 and 83% of the label found in the expired air, 1.3 and 8.9% of the label found as expired dioxane, and 4.1 and 7% found as expired CO_2 in animals receiving 10 and 1,000 mg/kg,

respectively. Elimination of 1,4-dioxane in both the expired air and in the urine appear to be first-order kinetic processes (Young et al. 1978a, 1978b).

3.4.4.3 Dermal Exposure

Data on the elimination of 1,4-dioxane following dermal exposure in humans and animals are not available.

3.4.4.4 Other Routes of Exposure

After a single intravenous dose of 10 mg/kg of 1,4-dioxane in rats, 4% of the dioxane was eliminated in the urine as dioxane, 92% as HEAA, and 1% was eliminated in the expired air (Young et al. 1978a, 1978b). Following a 1000 mg/kg dose, 11% was eliminated in the urine as dioxane, 60% as HEAA, and 27% in the expired air, indicating a dose-related shift in the elimination of the compound, possibly due to metabolic saturation. At low intravenous doses, 1,4-dioxane is eliminated from the plasma with apparently linear kinetics, while higher doses are eliminated progressively more slowly, achieving linear kinetics only after a non-linear phase, indicating the involvement of a saturable process, very likely metabolic saturation, in elimination of the compound. Elimination of 1,4-dioxane in both the expired air and in the urine following intravenous exposure appear to be first-order kinetic processes (Young et al. 1978a, 1978b). Pretreatment of rats with phenobarbital resulted in a 2.7-fold greater elimination of HEAA in the urine than in rats that were not pretreated (Woo et al. 1977c, 1978). The addition of DPEA partly reduced this effect, with the PB + DPEA animals eliminating 1.8-fold the HEAA of controls.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

Leung and Paustenbach (1990) Model.

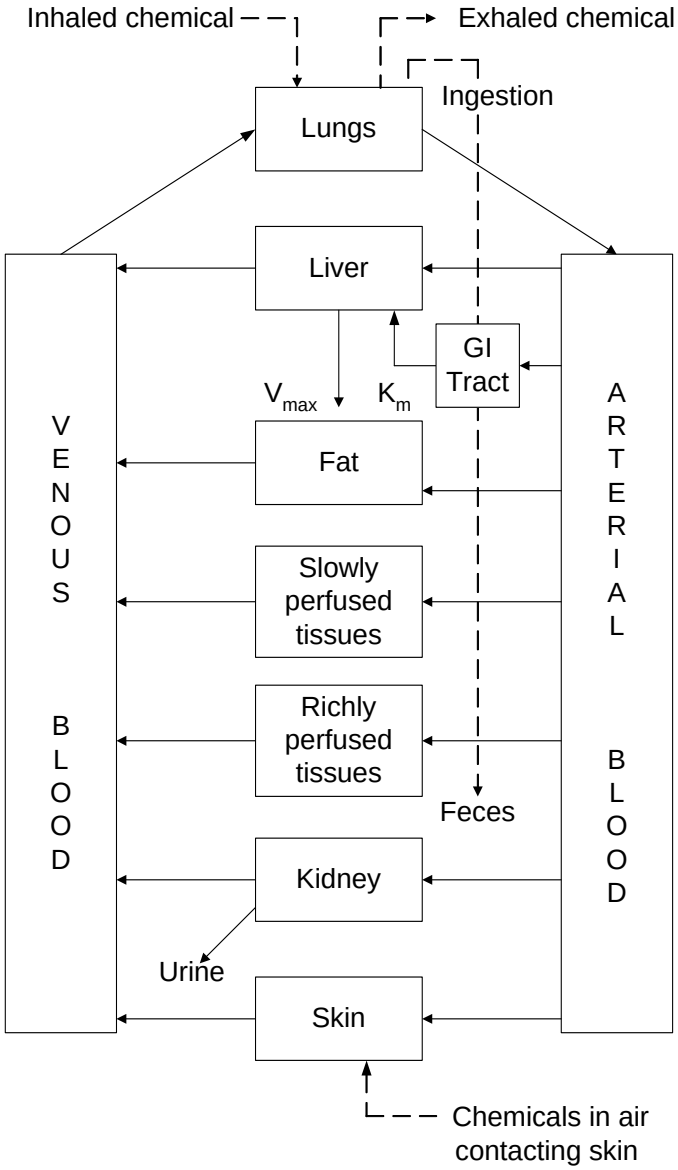
Leung and Paustenbach (1990) developed a PBPK model for 1,4-dioxane for rats and humans, based on the styrene model of Ramsey and Andersen (1984). The model simulates concentrations of 1,4-dioxane in the four modeled tissue compartments, as well as in arterial and venous blood, and the amount of metabolites formed.

Description of the Model. The model consists of compartments for liver, fat, slowly perfused tissues, and richly perfused tissues. Model parameters are presented in Table 3-6. Model inputs included inhalation, where 1,4-dioxane input was assumed to occur at a rate equal to the cardiac output, and drinking water, where 1,4-dioxane absorption was considered to be a zero-order process depositing 1,4-dioxane directly into the liver compartment. Tissue/air partition coefficients for rat blood, liver, fat, and muscle were determined by vial equilibration, and tissue/blood values were calculated by dividing the tissue/air coefficient by the blood/air coefficient. The richly perfused coefficient was set equal to that of the liver. Human coefficients were assumed to be identical to the rat. For the human model, alveolar ventilation rate and cardiac output were estimated using a $(\text{body weight})^{0.74}$ scalar. The metabolic constants were obtained by optimization of the model with experimental data from Young et al. (1977, 1978a, 1978b); these studies were also used to calibrate the model, using data on blood 1,4-dioxane levels, 1,4-dioxane in expired air, and urinary excretion of 1,4-dioxane and HEAA to compare with model predictions.

Validation of the Model. The model parameters were optimized against the rat and human data of Young et al. (1977, 1978a, 1978b). Comparisons of model simulations against data from studies other than those used in model development were not presented.

Risk Assessment. The model attempts to estimate concentrations of 1,4-dioxane in the blood and in the tissue compartments, as well as the levels of metabolites formed, following an inhalation or oral exposure to 1,4-dioxane. These internal dose surrogates could be used in the assessment of health risks from exposure to 1,4-dioxane. The study authors used liver tumor data from a rat study (Kociba et al.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Table 3-6. Parameters Used in the PBPK Model for 1,4-Dioxane

	Rat	Human
Weights		
Body (kg)	0.25	84.1
Liver (percent)	4	4
Fat (percent)	7	20
Richly perfused (percent)	5	5
Slowly perfused (percent)	75	62
Blood Flow		
Cardiac output (L/hour)	5.4	399
Liver (percent)	25	25
Fat (percent)	5	5
Richly perfused (percent)	51	51
Slowly perfused (percent)	19	19
Air flow		
Alveolar ventilation (L/hour)	5.4	399
Partition coefficients		
Liver/blood	0.85	0.85
Fat/blood	0.4	0.4
Richly perfused/blood	0.85	0.85
Slowly perfused/blood	0.54	0.2[a]
Metabolic constants		
Vmax	1.9[a]	300[a]
Km	7.5[a]	15[a]

[a]Values obtained by model optimization

Source: Adapted from Leung and Paustenbach (1990)

1974) to estimate risk-specific doses for tumor formation following oral exposure, fitting the rat data to a multistage model and using liver dioxane concentrations as the dose metric for conversion from rat to human values. Human risk levels calculated by dividing the rat value by 5.5 (a body surface area scaling factor) were compared with values calculated using the model to calculate a human equivalent concentration; the model values resulted in a 7–8-fold greater value for maximum likelihood exposure (MLE) risk values than did division of the rat values by 5.5. It is important to note that the application of a PBPK model only addresses differences in pharmacokinetic behavior between species, and that differences in pharmacodynamic behavior must be discussed separately.

Target Tissues. The model simulates concentrations of 1,4-dioxane in the four modeled tissue compartments, as well as in arterial and venous blood, and the amount of metabolites formed. While two of the compartments represent actual body tissues (liver, fat), it is not known whether the model's estimates of tissue concentrations of 1,4-dioxane in these tissues is representative of the actual concentration in the tissues. However, the model's predictions of metabolite formation have been calibrated with actual data, providing evidence that the estimate of internal dose to the liver (where all metabolism is assumed to occur) is accurate.

Species Extrapolation. The Leung and Paustenbach (1990) PBPK model for 1,4-dioxane was developed in rats and humans, and human data on the pharmacokinetics of 1,4-dioxane was used in the optimization of model parameters. As such, interspecies extrapolation using the two models should be possible, although it has not yet been presented.

Interroute Extrapolation. The model includes inputs for both inhalation and oral exposures, and as such, should provide a means to estimate an internal dose to a target tissue compartment or other dose metric regardless of which of these two exposure routes is used. The use of the model for interroute extrapolation is therefore feasible, although it has not yet been performed.

Reitz et al. (1990) Model.

Reitz et al. (1990) have also published a PBPK model for 1,4-dioxane in rats, mice, and humans, again building on the basic structure of the Ramsey and Andersen (1984) model for styrene. The model estimates concentrations of 1,4-dioxane in the modeled tissue compartments, as well as in arterial and venous blood, and the amount of metabolites formed.

Description of the Model. The model consisted of six compartments: lung, fat, liver, venous blood, slowly perfused tissues, and richly perfused tissues. The model was designed to simulate inhalation, intravenous, and oral exposures. Oral exposures could be by gavage or in the drinking water, and were assumed to pass through the liver before entering the systemic circulation. Intravenous injection was simulated by direct addition to the venous blood compartment, while inhalation deposited directly into arterial blood at a rate dependent on ventilation, cardiac output, and the blood/air partition coefficient for 1,4-dioxane. Tissue/air partition coefficients for 1,4-dioxane in human blood, rat blood, rat fat, rat muscle, and rat liver were determined by vial equilibration. Organ volumes, blood flows, and air flows were similar to those employed by Andersen et al. (1987), except that ventilation and cardiac output rates in humans were increased to provide a better simulation of the human blood level data. Metabolic rate constants were determined from data presented by Young et al. (1977, 1978a, 1978b) during optimization of the model. Metabolism was assumed to occur only in the liver, and metabolites were assumed to be removed from the system. Elimination of parent compound was modeled in the expired air and in the urine. The model parameters are presented in Table 3-7. After optimization using data from Young et al. (1977, 1978a, 1978b) the results of model runs and the corresponding experimental data were presented for venous blood concentrations in rats and humans following inhalation exposure, and venous blood concentrations in rats following intravenous exposure.

Validation of the Model. The model parameters were optimized against the rat and human data of Young et al. (1977, 1978a, 1978b). Comparisons of model simulations against data from studies other than those used in model development were not presented.

Risk Assessment. The model attempts to estimate concentrations of 1,4-dioxane in the blood and in the tissue compartments, as well as the levels of metabolites formed, following an inhalation, oral, or intravenous exposure to 1,4-dioxane. These internal dose surrogates could be used in the assessment of health risks from exposure to 1,4-dioxane. The study authors used the model to estimate “Human Virtually Safe Doses” (VSDs) based on tumor data from oral and inhalation studies in rats and mice (Kociba et al. 1974; NCI 1978; Torkelson et al. 1974). The VSDs were calculated by converting the rat no observable effect level (NOEL) for tumor formation to a human equivalent dose, and then dividing by a safety factor 100. The authors calculated a risk-specific water concentration of 20,000 µg/L for upper bound lifetime cancer risk of 1 in 100,000, calculated to represent the lower 95% confidence limit on administered dose producing a lifetime increase in risk of developing liver cancer, using the weighted average of area under the liver concentration/time curve and area under the metabolite concentration/time

Table 3-7. Parameters Used in the Reitz et al. (1990) PBPK Model for 1,4-Dioxane

	Mice	Rats	Humans
Body weight (kg)	0.035	0.400	70.0
Percentage of body weight			
Liver	4.0	4.0	3.1
Fat	4.0	7.0	23.1
Rapidly perfused	5.0	5.0	3.7
Slowly perfused	73.0	70.0	56.1
Blood	5.0	5.0	5.0
Flows (L/hour)			
Alveolar ventilation	2.34	7.61	696
Cardiac output	2.34	7.61	696
Percent of cardiac output			
Liver	25.0	25.0	25.0
Fat	5.0	5.0	5.0
Rapidly perfused	52.0	52.0	52.0
Slowly perfused	18.0	18.0	18.0
Partition coefficients			
Blood/air	2,750	1,850	3,650
Liver/air	1,557	1,557	1,557
Fat/air	851	851	851
Rapidly perfused/air	1,557	1,557	1,557
Slowly perfused/air	1,557	1,557	1,557
Saline/air	2,066	2,066	2,066
Metabolic constants (allometric)			
VmaxC (mg/hour)	10.0	13.7	6.35
Km (mg/L)	16.2	29.4	3.00
Miscellaneous constants			
Ka ($hour^{-1}$)	5.0	5.0	5.0
K_{ME} ($hour^{-1}$)	0.42	0.28	0.56
Water consumption (mL/day)	9.8	54	2,000

curve as the dose surrogate for conversion between species. It is important to note, however, that the application of a PBPK model only addresses differences in pharmacokinetic behavior between species, and that differences in pharmacodynamic behavior must be discussed separately.

Target Tissues. The model simulates concentrations of 1,4-dioxane in the four modeled tissue compartments, as well as in arterial and venous blood, and the amount of metabolites formed. While three of the compartments represent actual body tissues (liver, fat, venous blood), only for venous blood levels have experimental data been compared to model simulations. It is not known whether the model's estimates of tissue concentrations of 1,4-dioxane in the other tissues is representative of the actual concentration in the tissues. However, the model's predictions of metabolite formation have been calibrated with actual data, providing evidence that the estimate of internal dose to the liver (where all metabolism is assumed to occur) is accurate.

Species Extrapolation. The Reitz et al. (1990) PBPK model for 1,4-dioxane was developed for rats, mice, and humans. Human and rat data on the pharmacokinetics of 1,4-dioxane were used in the optimization of model parameters; mouse parameters were generally assumed to be equivalent to those in the rat. As such, interspecies extrapolation using the models for the different species should be possible.

Interroute Extrapolation. The model includes inputs for both inhalation, oral, and intravenous exposures, and as such, should be able to estimate an internal dose to a target tissue compartment or other dose metric regardless of which of these exposure routes is used. The use of the model for interroute extrapolation is therefore feasible, although it has not yet been performed.

Fisher et al. (1997) Model.

Fisher et al. (1997) have published a general PBPK model for volatile organic chemicals, which incorporates a compartment for elimination of the chemical in the breast milk. Model simulations predicted a high degree (18%) of lactational transfer of 1,4-dioxane. While the study authors note that the model is applicable to 1,4-dioxane, simulations using the model have not been compared to data from humans or animals exposed to 1,4-dioxane.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. The absorption of 1,4-dioxane following inhalation or oral exposure is rapid and essentially complete; absorption following dermal exposure is very low. The mechanisms involved in the absorption of 1,4-dioxane have not been evaluated, but given the speed of the absorption and the chemical similarity of 1,4-dioxane to other low-molecular-weight compounds, absorption is generally assumed to occur through passive diffusion.

Distribution. The mechanisms of distribution of 1,4-dioxane have not been evaluated. Data on the distribution of 1,4-dioxane are limited to studies following injection of the compound. In those studies, distribution of 1,4-dioxane was rapid (5–15 minutes to Tmax). 1,4-Dioxane has been detected in all tissues that have been evaluated, but has not been shown to appreciably accumulate in tissues, possibly due to its high water solubility.

Metabolism. Studies on the metabolism of 1,4-dioxane have clearly identified the primary metabolite as HEAA/1,4-dioxane-2-one, but have not confirmed a clear pathway for the formation of metabolites from 1,4-dioxane. Cytochrome P-450 enzymes are clearly involved, as evidenced by the studies of Woo et al. (1977c, 1978). It has been suggested that P-450-mediated metabolism may result in the formation of diethylene glycol, since injection of diethylene glycol in rats also results in the formation of HEAA (Woo et al. 1977a); however, additional data supporting this pathway have not been presented.

Excretion. The elimination of 1,4-dioxane occurs primarily (>95%) in the urine, as the primary metabolite, at low doses. At higher doses, metabolism becomes saturated, and a greater fraction is eliminated in the expired air; however, urinary elimination remains the primary method of elimination. Elimination of 1,4-dioxane in both the expired air and the urine following intravenous exposure appear to be first-order kinetic processes (Young et al. 1978a, 1978b). Evidence for active secretion or uptake of 1,4-dioxane from the kidney has not been reported.

3.5.2 Mechanisms of Toxicity

The mechanism of carcinogenicity of 1,4-dioxane has not been elucidated, but the results from several lines of investigation suggest that 1,4-dioxane has a non-genotoxic mode of action (Goldsworthy et al.

1991; Leung and Paustenbach 1990; Stott et al. 1981). Briefly, the collective evidence from evaluations of genetic toxicity suggests that 1,4-dioxane is unlikely to be genotoxic (see Section 3.3, Genotoxicity). 1,4-Dioxane was not mutagenic in bacterial assays with or without metabolic activation (Haworth et al. 1983; Khudoley et al. 1987; Morita and Hayashi 1998; Nestmann et al. 1984; Stott et al. 1981), did not induce chromosomal aneuploidy in yeast (Zimmermann et al. 1985), mutations in mouse lymphoma cells (Morita and Hayashi 1998; McGregor et al. 1991), or sex-linked recessive lethal mutations in *D. melanogaster* (Yoon et al. 1995). Moreover, in an occupationally study there was no evidence of an increased incidence of chromosomal aberrations among workers chronically exposed to relatively low levels of 1,4-dioxane compared to controls (Thiess et al. 1976). No significant increase in chromosomal aberrations was observed in Chinese hamster ovary cells incubated with 1,4-dioxane with or without metabolic activation, but there was a weak increase in sister chromatid exchanges when the cells were incubated without metabolic activation (Galloway et al. 1987). Also, incubation of BALB/3t3 cells with 1,4-dioxane resulted in transformations leading to the formation of foci, but at concentrations of 1,4-dioxane that were cytotoxic to over 50% of the cells (Sheu et al. 1998).

Several, structure-activity analyses have been conducted to study the mechanism of carcinogenicity of 1,4-dioxane. For example, a computerized structure relationship analysis using TOPKAT (version 3.0) in male rat and female mouse models showed a positive influence for the -O-CH_2- fragment of the molecule in both models, although the male rat model indicated that the symmetry of the 1,4-dioxane molecule plays a more substantial role in the carcinogenicity of 1,4-dioxane than the -O-CH_2- fragment (Blake 1995). An additional analysis of the potential role of 1,4-dioxane's metabolites HEAA and 1,4-dioxane-2-one predicted HEAA to be non-carcinogenic and non-mutagenic, but 1,4-dioxane-2-one was predicted to be strongly positive in the female mouse carcinogenicity model and the Ames mutagenicity model (Gombar 1995). A structure-activity relationship analysis using the Computer-Automated Structure Evaluation (CASE) methodology predicted that 1,4-dioxane would induce micronuclei in mice bone marrow cells as a result of the -O-CH_2- fragment. According to unpublished results cited by Rosenkranz and Klopman (1992), the concordance between experimental results and CASE predictions of the induction of micronuclei is in excess of 83%. However, Rosenkranz and Klopman (1992) indicated that the -O-CH_2- fragment does not seem to have intrinsic electrophilicity and could not suggest a possible DNA-reactive metabolite. This led them to suggest that the -O-CH_2- fragment might contribute to a non-genotoxic effect of 1,4-dioxane resulting in the induction of micronuclei. Since the experimental results of micronuclei-induction studies in mice have been mixed (McFee et al. 1994; Mirkova 1994; Morita and Hayashi 1998; Tinwell and Ashby 1994), Ashby (1994) suggested that it is not always possible to categorize a chemical as either unequivocally positive or negative in genotoxicity activity.

Numerous studies have examined the possible role of DNA damage, DNA synthesis, cell proliferation, or peroxisome proliferation in the carcinogenic effects of 1,4-dioxane. For instance, a test for DNA single strand breaks in rat hepatocytes incubated with 1,4-dioxane gave positive results, although only at cytotoxic concentrations (Sina et al. 1983). Stott et al. (1981) reported that hepatocytes from Sprague-Dawley rats dosed with 1,4-dioxane for 11 weeks showed no evidence of DNA alkylation or DNA repair activity, but showed increased levels of DNA synthesis. Based on these results, Stott et al. (1981) suggested that 1,4-dioxane induces tumors by a non-genetic mechanism.

The role of cell proliferation in the carcinogenicity of 1,4-dioxane was further evaluated in two studies that yielded inconclusive results. Administration of single doses of up to 2,000 mg 1,4-dioxane/kg by gavage to male Fischer 344 failed to induce replicative DNA synthesis in hepatocyte (Uno et al. 1994), which led the authors to suggest that 1,4-dioxane may induce liver cancer only in initiated cells. However, in a subsequent study by the same group of investigators, and using the same experimental protocol, 1,4-dioxane did increase hepatocyte cell proliferation (Miyagawa et al. 1999); the reason for the discrepancy in the results between the two studies is not apparent.

In liver tissue from Sprague-Dawley rats given single doses of 1,4-dioxane, there was a small but statistically significant amount of DNA damage (assessed by alkaline elution) at dose levels that did not induce cytotoxicity (Kitchin and Brown 1990, 1994). Liver toxicity was assessed by light microscopy and measurements of serum levels of ALT (no significant increase was observed). The DNA damage was accompanied by an increase in cytochrome P-450 content and by large increases in the activity of hepatic ornithine decarboxylase, suggesting a strong promoter activity for 1,4-dioxane.

Another study of the potential mechanisms of carcinogenicity of 1,4-dioxane showed that neither 1,4-dioxane nor the metabolite 1,4-dioxane-2-one induced DNA repair activity in primary rat hepatocytes following incubation *in vitro* with the chemicals (Goldsworthy et al. 1991). Administration of a single oral dose of 1,4-dioxane to Fischer 344 rats produced no evidence of hepatocyte DNA repair, did not increase DNA synthesis, relative liver weight or the activity of palmitoyl CoA oxidase (an indicator of peroxisome proliferation) (Goldsworthy et al. 1991). Furthermore, administration of a single dose of 1,000 mg/kg of 1,4-dioxane did not increase the hepatocyte labeling index 24 or 48 hours after dosing, but exposure to 1% 1,4-dioxane in the drinking water for 2 weeks resulted in a 2-fold increase in hepatic labeling index (Goldsworthy et al. 1991); the latter suggested that cell proliferation may play a role in the induction of liver carcinoma. In addition, no DNA repair activity or evidence of cells proliferation was

observed in nasal epithelial cells from rats administered 1% 1,4-dioxane in the drinking water for 2 weeks (Goldsworthy et al. 1991). However, it must be mentioned that Goldsworthy et al. (1991) acknowledged that a 2-week period of exposure might have been too short for detecting a proliferative response. Goldsworthy et al. (1991) concluded that the mechanism of carcinogenicity of 1,4-dioxane remains obscure and may involve a novel mechanism.

Gold et al. (1993) analyzed 351 chemicals in the Carcinogenic Potency Database (CPDB) and pointed out that, relative to non-mutagenic chemicals, mutagens are more likely to be carcinogenic, more likely to induce tumors at multiple target sites and, more likely to be carcinogenic in two species. Since 1,4-dioxane was carcinogenic in more than one species and induced tumors at multiple sites, one would expect that 1,4-dioxane would behave like a mutagen, but the empirical data suggest otherwise. Gold (1993) pointed out that among the CPDB chemicals tested for mutagenicity 75% are mutagens compared to 45% for non-mutagens and suggested that administration of large doses in cancer bioassays result in mitogenesis, which in turn increases the rate of mutagenesis and thus carcinogenesis.

The lack of significant genotoxicity along with the cytotoxicity observed at dose levels that induce tumors support the view that 1,4-dioxane acts via an unknown non-genotoxic mechanism.

The mechanism(s) by which 1,4-dioxane induces kidneys lesions is not known and virtually no discussion about this topic was found in the available reviews. The findings in the cases described by Barber (1934) and Johnstone (1959) are consistent with an acute nephritic syndrome, which is characterized by acute renal failure and oliguria. The impaired glomerular filtration rate causes extracellular fluid volume expansion, edema, and hypertension. A study of controlled exposures in volunteers showed that 1,4-dioxane has poor renal clearance, 0.34 mL/minute (Young et al. 1977), which probably contributes to accumulation of the chemical in the kidneys as biotransformation to the metabolite HEAA becomes saturated under conditions of high exposure.

3.5.3 Animal-to-Human Extrapolations

Exposure to high concentrations of 1,4-dioxane induces liver and kidneys effects in humans and in animals, regardless of the route of exposure. Based solely on the similarity of target organs, it would appear that results from animal studies could be used as valid models to predict health effects in humans resulting from high-dose exposure to 1,4-dioxane.

Long-term oral exposure of rodents to 1,4-dioxane has induced liver tumors in rats and mice as well as tumors in the nasal cavity of rats (JBRC 1998c; Kociba et al. 1974; NCI 1978). Therefore, the issue is whether these long-term, relatively high-exposure studies in animals are relevant to the low environmental exposures to 1,4-dioxane experienced by the general population. Studies of humans exposed chronically to relatively low concentrations of 1,4-dioxane in the air in occupational settings have provided no evidence of ill effects among the workers, including cancer, associated with 1,4-dioxane (Buffler et al. 1978; Thiess et al. 1976). However, it is unclear if the effects reported in humans are consistent with the potency estimated in rodents.

Some studies have shown that the liver tumors in rats are accompanied by extensive toxicity, as evidenced by hepatocyte hyperplasia, accumulation of fat in the cytoplasm, and degenerative changes (JBRC 1998c; Kociba et al. 1974; NCI 1978), which has led some to suggest that cell damage and degeneration may be a necessary occurrence for the formation of liver tumors in rats. Since liver toxicity in rats seems to occur only at dose levels at which plasma clearance and excretion of HEAA are reduced, and plasma concentrations of unchanged 1,4-dioxane are increased, it may be appropriate to consider the differences in metabolic disposition when extrapolating from effects that occur only with high doses to low-dose events (Kociba et al. 1975).

The relevance to humans of the nasal lesions and nasal tumors consistently seen in rats following exposure to 1,4-dioxane through the drinking water in many studies has been questioned (Stickney et al. 2003). Goldsworthy et al. (1991) suggested that the tumors resulted from inspiration of water containing 1,4-dioxane into the nasal cavity. Preliminary studies with a dye in the drinking water demonstrated that large amounts of inhaled water may be deposited directly in the nose as the animals drink (Reitz et al. 1990). The lack of nasal tumors in mice in chronic drinking water studies could be due to differences in tissue sensitivity and/or repair mechanisms, or to differences in anatomical features. However, species differences are difficult to establish since 1,4-dioxane acts via an unknown mechanism to produce tumors in liver, nasal cavity, and other sites.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals

with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Based on the available information, there is no evidence that 1,4-dioxane is an endocrine disruptor in humans or in animals, but appropriate tests have not been conducted. The only relevant information that was located is that 1,4-dioxane tested negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). A substance was considered positive when its activity was more than 10% of the activity of 10^{-7}M 17β-estradiol.

Long-term oral studies have found no histopathologic (non-neoplastic) alterations in endocrine glands and reproductive organs from rats and mice (Kociba et al. 1974; NCI 1978), and the same was found in a chronic-duration inhalation study in rats (Torkelson et al. 1974). However, neoplasms associated with the

administration of 1,4-dioxane occurred in the testis/epididymis in male rats administered ≥240 mg 1,4-dioxane/kg/day in the drinking water for 2 years (NCI 1978). Another 2-year bioassay reported an increased incidence of mammary gland adenomas in rats treated in the drinking water with 514 mg 1,4-dioxane/kg/day (JBRC 1998c).

Standard reproductive toxicity studies on 1,4-dioxane were not located and only one study that examined the developmental effects of 1,4-dioxane was available (Giavini et al. 1985). The latter reported slight fetotoxicity occurring at a dose level that also affected the mothers.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are

proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are no studies that specifically address the health effects of exposure to 1,4-dioxane in children or in immature animals; therefore, it is unknown whether children differ from adults in their susceptibility to health effects from 1,4-dioxane. Data in adults were derived from occupational studies (Barber 1934; Buffler et al. 1978; Thiess et al. 1976) and studies in volunteers (Fairley et al. 1934; Silverman et al. 1946; Yant et al. 1930; Young et al. 1977). The former showed that exposure to high concentrations of 1,4-dioxane in the air (and also dermally) can severely damage the liver and kidneys and can be lethal. The studies of controlled exposure with volunteers showed that exposure to 1,4-dioxane in the air can produce eye, nose, and throat irritation. It is reasonable to assume that the same types of effects would be seen in children accidentally exposed to high amounts of 1,4-dioxane.

There is no information regarding possible adverse developmental effects in humans exposed to 1,4-dioxane. A study in rats exposed orally to 1,4-dioxane during gestation found slight fetotoxicity, but at a dose level that also affected the mothers (Giavini et al. 1985). There is evidence that 1,4-dioxane is at

most a weak genotoxic compound. Therefore, it is unlikely that parental exposure would result in adverse childhood development or cancer development as a result of 1,4-dioxane metabolite exposures to parental germ cells.

There is no information regarding pharmacokinetics of 1,4-dioxane in children. Analysis of urine samples from humans exposed to 1,4-dioxane suggests the involvement mainly of phase I metabolic enzymes in the biotransformation and elimination of 1,4-dioxane. The specific P-450 isozymes involved in phase I metabolism are not known, and thus, no conclusions can be drawn based on general differences in isozymes activities between adults and children. However, if the enzymes in question are lower in neonates and oxidation of 1,4-dioxane is a detoxification reaction, this could result in greater toxicity in neonates. It is not known whether 1,4-dioxane can cross the placenta and there are no reports on levels of 1,4-dioxane in maternal milk.

There are no biomarkers of exposure or effect for 1,4-dioxane that have been validated in children or in adults exposed as children. No relevant studies were located regarding interactions of 1,4-dioxane with other chemicals in children or adults.

No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to 1,4-dioxane, reducing body burden, or interfering with the mechanisms of action for toxic effects.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and

interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,4-dioxane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,4-dioxane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations that are Unusually Susceptible.”

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,4-Dioxane

1,4-Dioxane and its metabolite, HEAA, were found in the urine of workers exposed to a time-weighted average air concentration of 1.6 ppm of 1,4-dioxane for 7.5 hours (Young et al. 1976). The concentration of HEAA was 414 µmol/L and that of unchanged 1,4-dioxane was only 3.5 µmol/L, suggesting rapid and extensive metabolism. 1,4-Dioxane in the urine is a specific biomarker for exposure to 1,4-dioxane, but HEAA can also be produced by exposure to 1,4-dioxane-2-one and diethylene glycol. In a controlled-exposure study with volunteers exposed to 50 ppm 1,4-dioxane vapors for 6 hours, the half-life for elimination of 1,4-dioxane from plasma was 59 minutes (Young et al. 1977). The plasma concentration

of HEAA reached a peak at about 1 hour after exposure ceased and decreased linearly thereafter. Of all the 1,4-dioxane detected in the urine within a 48-hour period, 90% was excreted during the exposure period and none could be detected 6 hours after termination of the exposure. The half-life for elimination of 1,4-dioxane in the urine was 48 minutes, and that of HEAA was 2.7 hours. Almost all the 1,4-dioxane was excreted in the urine as HEAA. About half of the total HEAA excreted was excreted during the exposure period and the excretion was complete 18 hours after the exposure ceased. A simulation of repeated exposures to 50 ppm 1,4-dioxane for 8 hours/day showed that 1,4-dioxane will reach a peak in plasma at the end of each exposure day and will not accumulate; neither will HEAA. Collectively, these results imply that 1,4-dioxane and HEAA in plasma and urine can be used as biomarkers of recent isolated exposure or multiple daily exposures, but that could not differentiate between the two types of exposure (providing the exposure concentrations are below about 50 ppm). In addition, because these substances are rapidly eliminated, they cannot be used as biomarkers of past exposure to 1,4-dioxane. Given the low levels of 1,4-dioxane reported in the environment, it is not unlikely that the levels of 1,4-dioxane and HEAA in members from the general population fall under the detection levels of the available analytical methods.

Some chemicals bind to macromolecules (i.e., DNA, hemoglobin, etc.) to form compounds that can be used as specific biomarkers of exposure. That is not the case for 1,4-dioxane. In liver preparations from rats administered a single intraperitoneal dose of radioactive 1,4-dioxane, most of the radioactivity was bound non-covalently in the cytosol (Woo et al. 1977b). Covalent binding to macromolecules was highest in nuclear fraction followed by mitochondrial, microsomal, whole homogenate, and cytosol fractions. The binding was nonspecific and not associated with DNA. Pretreatment of rats with microsomal enzyme inducers had no significant effect on the covalent binding to macromolecules. There was no microsomally-mediated binding of radioactivity to DNA.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,4-Dioxane

The liver and kidneys are targets for 1,4-dioxane toxicity, but lesions to these organs cannot be considered specific biomarkers for 1,4-dioxane because exposure to many different chemicals or health conditions unrelated to chemical exposures can produce similar effects.

3.9 INTERACTIONS WITH OTHER CHEMICALS

The only information located that is relevant to environmental or occupational exposures is that from a study by Buffler et al. (1978) in workers, even though it provides only suggestive evidence that interactions may have played a role in the outcome. In a cohort of 165 workers exposed intermittently to concentrations of 1,4-dioxane between 0.1 and 17 ppm, seven deaths were identified among those working in the manufacturing area and five among those involved in the processing area (Buffler et al. 1978). The exposure histories of the seven subjects indicated that all were exposed to other chemicals of possible significance at earlier times and for longer intervals than their exposure to 1,4-dioxane. In addition, the five deaths that occurred among the processing area were exposed to vinyl chloride simultaneously with their exposure to 1,4-dioxane. No firm conclusions can be drawn from this study regarding interactions of 1,4-dioxane with other chemicals.

If cytochrome CYP2E1 is involved in the metabolism of 1,4-dioxane (cytochrome P-450 is known to be involved in 1,4-dioxane metabolism, but the specific isozymes are not known), then ethanol could alter the hepatic effects of 1,4-dioxane if one assumes that the toxic entity is a metabolite of 1,4-dioxane. In the Thiess et al. (1976) study, some workers exposed to 1,4-dioxane who consumed alcohol frequently had elevated serum levels of transaminases; however, the values became normal after the workers reduced their alcohol consumption, suggesting that the elevated transaminase values were purely due to exposure to ethanol and not to the combination of 1,4-dioxane and ethanol, at least at the relative low level of exposure experienced by the workers in this occupational study (maximum 14.3 ppm).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,4-dioxane than will most persons exposed to the same level of 1,4-dioxane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,4-dioxane, or compromised function of organs affected by 1,4-dioxane. Populations who are at greater risk due to their unusually high exposure to 1,4-dioxane are discussed in Section 6.7, Populations with Potentially High Exposures.

Because 1,4-dioxane is a liver and kidney toxicant at high concentrations, people with compromised liver or kidneys function may be more susceptible to the effects of exposure to 1,4-dioxane than healthy

individuals. Among those unusually susceptible would be, for example, individuals who drink excessive amounts of alcohol, those on medications known to affect the liver or the kidneys, or those with genetic diseases of the kidney.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,4-dioxane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,4-dioxane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No texts were found that provided specific information about treatment following exposure to 1,4-dioxane.

3.11.1 Reducing Peak Absorption Following Exposure

The only relevant information that was located is that the skin and eyes should be immediately flushed with water for at least 15 minutes following skin and eye contact (NIOSH 1977). If 1,4-dioxane is swallowed, vomiting should be induced immediately if the patient is conscious (NIOSH 1977).

3.11.2 Reducing Body Burden

No information was located regarding reducing body burden following exposure to 1,4-dioxane. As mentioned in Section 3.4, Toxicokinetics, 1,4-dioxane and its main metabolites do not accumulate and are rapidly eliminated from the body in the urine.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The liver and kidneys are targets for 1,4-dioxane toxicity in humans and animals. Lesions have been found in humans acutely exposed to relatively high concentrations of 1,4-dioxane and in animals following inhalation, oral, and dermal exposure (see Section 3.2). Also, 1,4-dioxane has induced liver

cancer in rats and mice and nasal cancer in rats. The mechanism(s) of toxic action of 1,4-dioxane has not been elucidated, but there is increasing evidence that the liver lesions seen in animals evolve into neoplasms induced by 1,4-dioxane through a non-genotoxic mechanism of action. Any attempt to discuss possible mechanisms to interfere with this action would be pure speculation at this time.

3.12 ADEQUACY OF THE DATABASE

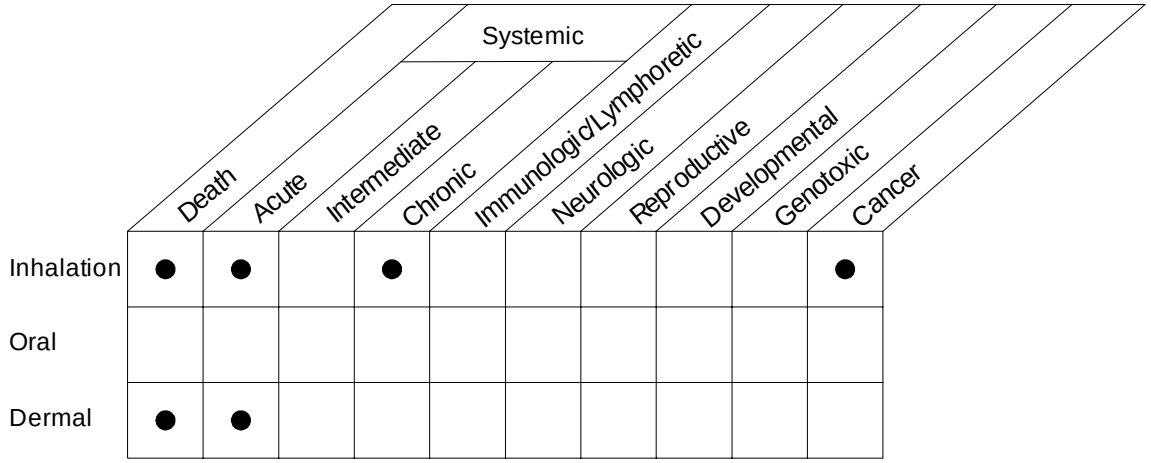
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,4-dioxane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,4-dioxane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

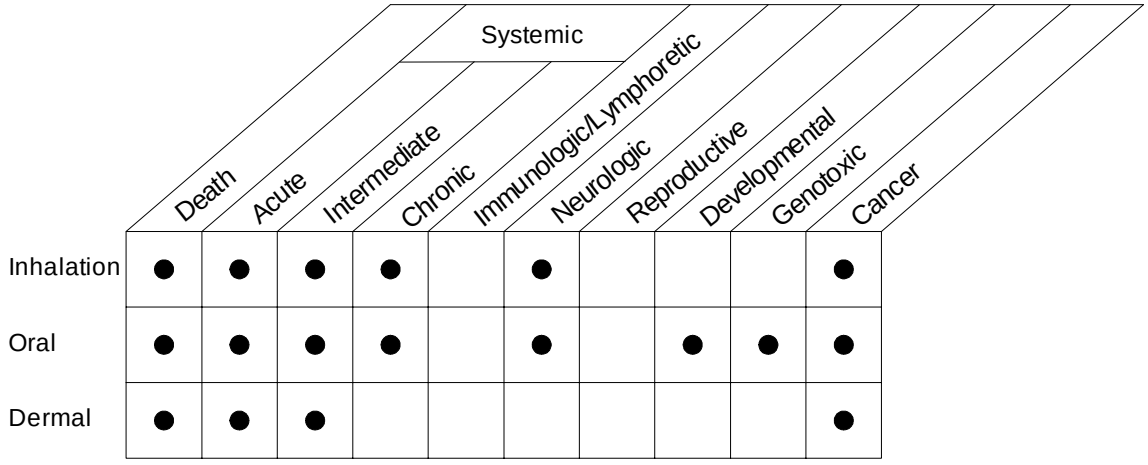
3.12.1 Existing Information on Health Effects of 1,4-Dioxane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,4-dioxane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,4-dioxane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-5. Existing Information on Health Effects of 1,4-Dioxane



Human



Animal

● Existing Studies

As shown in Figure 3-5, there is limited information on the effects of 1,4-dioxane in humans. The available information is derived from occupational studies in which exposure was assumed to have been primarily by inhalation of vapors, but that may have also involved dermal exposure. These studies provided information on acute systemic effects and lethality and also effects due to long-term exposure. A few studies of controlled inhalation exposures with volunteers are also available and these studies provided data on acute systemic effects. No information was located regarding oral exposure of humans to 1,4-dioxane.

In animals, the studies available for review provided information on lethality and on systemic, neurological, and cancer effects following inhalation exposure to 1,4-dioxane. For oral exposure, there are studies that evaluated systemic, neurological, developmental, genotoxic, and cancer effects. No studies were available regarding chronic systemic effects, or immunological, neurological, reproductive, developmental, or genotoxic effects after dermal exposure to 1,4-dioxane.

The information available from human and animals studies suggests that the effects of 1,4-dioxane are not route-dependent. In addition, the limited environmental monitoring data available suggests that the levels of 1,4-dioxane to which the general population might be exposed through contact or use of consumer products (including food), or that are normally found in environmental media are generally orders of magnitude lower than those used in studies with experimental animals.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Two occupational studies provided acute inhalation data for 1,4-dioxane, Barber (1934) and Johnstone (1959). Barber (1934) described five lethal cases among factory workers exposed to 1,4-dioxane, whereas Johnstone (1959) described one additional lethal occupational case in which dermal exposure also occurred. Exposure to unknown, but lethal concentrations of 1,4-dioxane produced serious liver and kidney effects. A few additional studies in volunteers evaluated mostly clinical signs, such as eye and nose irritation, during exposures varying from 3 minutes to 6 hours (Fairley et al. 1934; Silverman et al. 1946; Yant et al. 1930; Young et al. 1977). The lowest concentration that produced an effect was 50 ppm during a 6-hour exposure, which caused eye irritation (Young et al. 1977). Data from the study by Young et al. (1977) were used to derive an acute-duration inhalation MRL for 1,4-dioxane. The animal database consists mainly of early studies in rodents exposed to lethal or near lethal concentration of 1,4-dioxane that indicated that the liver and kidneys are

the main targets of 1,4-dioxane toxicity in animals (Fairley et al. 1934; Yant et al. 1930). Additional acute inhalation studies conducted according to current guidelines would be helpful to establish dose-response relationships for liver and kidney effects at low levels of exposure. No data were located regarding acute oral exposure of humans to 1,4-dioxane. Most studies in animals provided lethal dose levels and also showed that the liver and kidneys are the organs most severely affected by high oral doses of 1,4-dioxane (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Schrenk and Yant 1936; Smyth et al. 1941). A more recent 2-week drinking water study in rats, although with limitations, provided sufficient information on systemic end points and was used as the basis for derivation of an acute-duration oral MRL for 1,4-dioxane (JBRC 1998a). Additional acute oral studies conducted according to current guidelines could provide information on thresholds for liver and kidney effects. Also, exposures to low or moderate single oral doses followed by long observation periods would provide information on reversibility of the effects. Limited acute dermal data were found. In the lethal occupational case described by Johnstone (1959), considerable dermal exposure occurred since the subject used to wipe his hands with 1,4-dioxane to clean them; this probably contributed to the liver and kidney toxicity observed. In the studies with volunteers mentioned above, eye irritation was most likely due to direct contact of the eye with the vapors of 1,4-dioxane and not due to inhaled 1,4-dioxane. A study in rats applied a dose of 8,300 mg/kg of 1,4-dioxane to a shaved area of the skin found no signs of skin irritation during a 14-day observation period (Clark et al. 1984). Additional acute dermal studies may be tied to studies of the pharmacokinetics of 1,4-dioxane by this route of exposure, which has not been well characterized.

Intermediate-Duration Exposure. No intermediate-duration studies in humans were available. An early study by Fairley et al. (1934) in several animal species provided enough information to determine that the liver and kidneys are targets for 1,4-dioxane toxicity. The lowest concentration of 1,4-dioxane to which rats, mice, and guinea pigs were exposed intermittently for 3–12 weeks was 1,000 ppm, which caused moderate to severe kidney toxicity. Because of the severity of the effects, this information was considered inadequate for derivation of an intermediate-duration inhalation MRL. However, the chronic-duration inhalation MRL (see below) was also adopted as the intermediate-duration inhalation MRL. Several oral studies in animals provided information on lethal doses (Fairley et al. 1934; Kociba et al.1974) and on systemic effects, mostly hepatic and renal (Fairley et al. 1934; Lundberg et al. 1987; Stott et al. 1981). A more recent 90-day drinking water study in rats provided sufficient information on multiple end points and was used as the basis (liver effects) for an intermediate-duration oral MRL for 1,4-dioxane (JBRC 1998b). Information by the dermal route of exposure was limited to a study of intermittent application of 1,4-dioxane to the skin of rabbits and guinea pigs for up to 101 days (Fairley et al. 1934). There were no dermal effects in either species at dose levels that induced liver and kidney

lesions, which appeared to be more severe in rabbits than in guinea pigs. Although the target organs following inhalation exposure are known, additional inhalation studies with lower concentrations of 1,4-dioxane and following current testing standards are needed to establish dose-response relationships for liver and kidney effects and to obtain more information on possible effects on other organs (e.g., reproductive organs, endocrine glands). Information on effects on other organs is also limited in intermediate oral studies. The use of PBPK models for 1,4-dioxane (Leung and Paustenbach 1990; Reitz et al. 1990) may obviate the need for additional studies by multiple routes of exposure, since target organ concentrations obtained following exposure by one route may be used to back estimate exposure concentrations by a different route.

Chronic-Duration Exposure and Cancer. An occupational study of workers exposed to 1,4-dioxane provides information regarding long-term exposure to this chemical. Thiess et al. (1976) found no adverse effects in workers exposed to 0.006–14.3 ppm 1,4-dioxane for an average of 25 years. Only one chronic-duration study by the inhalation route was available (Torkelson et al. 1974). This study provided information on multiple organs and tissues, and hematology parameters in rats; no adverse effects were found. This study was used to derive a chronic-duration inhalation MRL for 1,4-dioxane. Because only one exposure level was used, the true NOAELs for the various organs and systems are unknown and may be higher. Therefore, additional studies in animals exposed to higher concentrations of 1,4-dioxane may be necessary to fill this data gap. Also, as mentioned above, PBPK models may be used to extrapolate data from the chronic oral studies to inhalation exposure situations. Several chronic-duration oral studies in rats and mice are available (JBRC 1998c; Kociba et al. 1974; NCI 1978). These studies provided information on clinical signs, changes in body weight, hematology, blood chemistry, urinalysis, and gross and microscopic appearance of major organs and tissues. The liver and kidneys were the main targets for 1,4-dioxane toxicity. A NOAEL of 9.6 mg/kg/day for liver effects in male Sherman rats was used to derive a chronic-duration oral MRL for 1,4-dioxane (Kociba et al. 1974). Additional chronic oral studies do not seem necessary at this point. No chronic dermal studies were located, but it is not apparent what new key information such studies could provide.

Very limited information was found regarding human exposure to 1,4-dioxane and cancer. A study of 165 workers exposed intermittently to 0.1–17 ppm 1,4-dioxane for up to 21 years found no significant increases in the incidences of deaths due to cancer (Buffler et al. 1978). 1,4-Dioxane was not carcinogenic in rats in the only single inhalation bioassay (Torkelson et al. 1974). However, only one exposure level was used; therefore, a dose-response relationship for cancer could not be estimated. Long-term oral administration of 1,4-dioxane induced liver cancer in rats and mice and also nasal tumors in rats

(Argus et al. 1965, 1973; Hoch-Ligeti et al. 1970; JBRC 1998c; Kociba et al. 1974; NCI 1978). 1,4-Dioxane was not a complete carcinogen in a 60-week dermal exposure study in mice (King et al. 1973), but showed promoter activity in oral (Lundberg et al. 1987) and dermal studies (King et al. 1973). 1,4-Dioxane was not an initiator in a dermal assay in mice (Bull et al. 1986). Additional bioassays will probably not provide any new key information at this time, but since the mechanism of carcinogenicity of 1,4-dioxane is yet unknown, continued research on this topic and on the role of metabolism in carcinogenicity is necessary. Some have suggested that the cancer risk assessment for 1,4-dioxane be updated (Stickney et al. 2003). Specifically, it has been suggested that the nasal tumors in rats, which is the basis for the current oral slope factor derived by EPA (IRIS 2004), are not relevant for human exposure because they result from water entering the nasal cavity when the animals drink from sipper bottles. Also, the PBPK modeling studies of Leung and Paustenbach (1990) and Reitz et al. (1990) have been applied to estimate the internal dose and the potential human cancer risks. Finally, the use of a nonlinear approach to low dose extrapolation might be considered based on the observations that liver toxicity, which some have suggested may be required for tumor development, occurs only at doses above which the metabolism of 1,4-dioxane is saturated. The EPA is currently re-evaluating the health assessment for 1,4-dioxane (EPA 2004f).

Genotoxicity. The genotoxic effects of 1,4-dioxane have been well characterized in studies *in vitro* in microorganisms (Haworth et al. 1983; Hellmer and Bolcsfoldi 1992; Khudoley et al. 1987; Kwan et al. 1990; Morita and Hayashi 1998; Nestmann et al. 1984; Stott et al. 1981; Zimmermann et al. 1985) and in mammalian cells (Galloway et al. 1987; Goldsworthy et al. 1991; McGregor et al. 1991; Morita and Hayashi 1998; Sheu et al. 1988). Most of these studies were conducted both in the presence and absence of metabolic activation systems, which would suggest that metabolites of 1,4-dioxane also are not mutagenic. The results from studies *in vivo* also provided mostly negative evidence of genotoxicity (Goldsworthy et al. 1991; Kitchin and Brown 1990, 1994; McFee et al. 1994; Mirkova 1994; Morita and Hayashi 1998; Muñoz and Barnett 2002; Stott et al. 1981; Tinwell and Ashby 1994; Yoon et al. 1985). The total weight of evidence suggests that 1,4-dioxane is either a weak genotoxin or not genotoxic, and it is unlikely that further studies will provide new information.

Reproductive Toxicity. No information was located regarding reproductive effects of 1,4-dioxane in humans. There are studies that examined the gross and microscopic appearance of the reproductive organs from rats following chronic inhalation exposure (Torkelson et al. 1974) and from rats and mice following intermediate oral exposure (JBRC 1998b) and chronic oral exposure to 1,4-dioxane (JBRC 1998c; Kociba et al. 1974; NCI 1978), but no assessments of reproductive function or examinations of

sperm characteristics have been made. The lack of effects on reproductive organs observed in these studies diminishes the need to conduct a 2-generation reproductive study. In addition, only one study was located that tested the estrogenic properties of 1,4-dioxane in an assay *in vitro* (Nishihara et al. 2000), with negative results. Additional standard *in vivo* and *in vitro* studies to assess whether 1,4-dioxane has endocrine disruptor properties would be useful.

Developmental Toxicity. There is no information on developmental effects in humans exposed to 1,4-dioxane. If populations were identified that are exposed to high levels of 1,4-dioxane, it would be useful to determine whether 1,4-dioxane or metabolites are found in breast milk. This can also be done in surveys monitoring chemicals in the general population at the national level. Only one study was located that evaluated developmental parameters in rats exposed orally by gavage during gestation (Giavini et al. 1985). Slight fetotoxicity was seen at a dose level that affected the mothers. Additional studies are necessary to determine whether adverse developmental effects can occur without maternal toxicity. In addition, a developmental neurotoxicity study in rats in which pups are tested at various ages after being exposed *in utero* and/or via maternal milk would fill a data gap.

Immunotoxicity. No information was located regarding immunotoxic effects in humans following exposure to 1,4-dioxane. The information from animal studies is restricted to gross and microscopic examination of lymph nodes and the spleen from rats exposed intermittently to 111 ppm 1,4-dioxane vapors for 2 years (Torkelson et al. 1974) and of the lymph nodes, spleen, and thymus from rats and mice dosed with up to 2,700 mg 1,4-dioxane/kg/day in the drinking water for 13 weeks (JBRC 1998b), or in rats and mice dosed with up to 1,599 mg 1,4-dioxane/k/day in the drinking water for up to 2 years (JBRC 1998c; Kociba et al. 1974; NCI 1978). No treatment-related effects were observed. Although there was no indication that immunocompetence was compromised in these studies, a study performing a complete Tier I battery of tests may be warranted to evaluate the possibility that exposure to 1,4-dioxane might cause subtle alterations in immune parameters.

Neurotoxicity. Edema of the brain was observed in lethal cases of intoxication with 1,4-dioxane vapors (Barber 1934; Johnstone 1959). Occupational studies of long-term exposure to lower concentrations of 1,4-dioxane did not report signs or symptoms that would indicate neurological damage, but sensitive tests were not conducted (Buffler et al. 1978; Thiess et al. 1976). Exposure of mice and rats for 4 hours to 1,800–2,400 ppm 1,4-dioxane had a narcotic effect (Frantik et al. 1994) and exposure to 3,000 ppm intermittently for 2 weeks affected an avoidance response in rats (Goldberg et al. 1964), which also could have been due to narcosis. High oral doses also induced narcosis in rabbits (Knoefel 1935).

Vacuolar changes were observed in the brain from rats exposed to 2,750–2,960 mg 1,4-dioxane/kg/day for 2 weeks (JBRC 1998a) and from rats exposed to 1,900–2,010 mg/kg/day for 13 weeks (JBRC 1998b). Long-term inhalation (Torkelson et al. 1974) and oral studies (JBRC 1998c; Kociba et al. 1974; NCI 1978) in rats and mice have provided no indication of adverse clinical signs in the animals and examination of the brain, spinal cord, and sciatic nerve was unremarkable. The overall information suggests that 1,4-dioxane may have narcotic properties at high concentrations, but it would be useful to determine whether possible subtle behavioral effects can be detected with more sensitive tests at exposure concentrations that do not induce narcosis.

Epidemiological and Human Dosimetry Studies. Information on the health effects of 1,4-dioxane in humans is derived from cases of accidental exposure at work to relatively high concentrations of 1,4-dioxane, which caused death (Barber 1934; Johnstone 1959), and studies of long-term exposure, also at work, to lower concentrations of 1,4-dioxane (Buffler et al. 1978; Thiess et al. 1976). Follow-up evaluations of individuals who may have been occupationally exposed would provide valuable information. No specific group from the general population that may have been subjected to unusually high amounts of 1,4-dioxane was identified. If such a situation arises, for example due to an accidental spill or leak from a waste site resulting in contaminated water or soil, individuals potentially exposed to 1,4-dioxane should be monitored for liver and kidney effects with standard function tests, since the liver and the kidneys have been identified as targets for 1,4-dioxane toxicity.

Biomarkers of Exposure and Effect.

Exposure. 1,4-Dioxane and its main metabolite, HEAA, have been identified in the blood and urine from workers exposed to 1,4-dioxane vapors (Young et al. 1976) and from volunteers exposed to controlled amounts 1,4-dioxane vapors (Young et al. 1977). Under condition of low to moderate exposure, the transformation of 1,4-dioxane to HEAA is rapid and extensive, and HEAA is rapidly eliminated in the urine (Young et al. 1977). The development of models that would support quantitative estimates of exposure to 1,4-dioxane based on urine levels of HEAA may be valuable in cases of high exposure, but given the very low levels of 1,4-dioxane that the general population is exposed to, the development of analytical methods capable to detect and quantify HEAA in the general population may be more useful.

Effect. There are no biomarkers of effect specific for 1,4-dioxane. Exposure to high amounts of 1,4-dioxane affects the liver and kidneys, but no 1,4-dioxane-induced health effects have been reported in

populations exposed to low amounts of 1,4-dioxane (Buffler et al. 1978; Thiess et al. 1976). Research to identify reliable biomarkers for exposure to 1,4-dioxane in humans would be useful in order to evaluate the prevalence and magnitude of exposure in an at-risk population.

Absorption, Distribution, Metabolism, and Excretion. Among the areas of absorption, distribution, metabolism, and excretion, the greatest data need lies in metabolism; specifically, the determination of the metabolic pathways involved in the metabolism of 1,4-dioxane to its primary metabolite, HEAA or 1,4-dioxane-one (Braun and Young 1977; Woo et al. 1977a, 1977b, 1977c; Young et al. 1977). While the identity of the metabolite has been determined and the involvement of cytochrome P-450 enzymes has been demonstrated (Woo et al. 1977c, 1978), the formation of intermediate metabolites, and their identities, has not been demonstrated. Additional information regarding this pathway may be useful in the refinement of PBPK models and in the development of biomarkers of exposure and/or effect. Data are lacking on the absorption of 1,4-dioxane in humans following oral and dermal exposure, but this information would likely do little to further our understanding of the pharmacokinetic processes of 1,4-dioxane.

Comparative Toxicokinetics. Studies directly comparing the toxicokinetics of 1,4 dioxane across species are not available. Some limited data on 1,4-dioxane absorption following inhalation exposure suggest large differences in the absorbed dose, expressed on a per body weight basis, between rats and humans (Young et al. 1977, 1978a, 1978b). However, these studies did not measure absorption efficiencies. Studies examining absorption efficiency in humans and rats following inhalation and oral exposures would provide valuable data for evaluating possible species differences. The available data on metabolism and elimination of 1,4 dioxane in humans and rats indicate that the compound behaves similarly in the two species (Woo et al. 1977a, 1977b, 1977c, 1978; Young et al. 1976, 1977, 1978a, 1978b). The available PBPK models for 1,4 dioxane also indicate that the behavior of 1,4 dioxane is similar in rats and humans. Studies of the toxicokinetic behavior of 1,4 dioxane in animal species other than the rat would provide additional insight into potential interspecies differences, while studies directly comparing the toxicokinetic behavior of 1,4 dioxane in multiple species would add to our understanding of the comparative toxicokinetic behavior of 1,4 dioxane.

Methods for Reducing Toxic Effects. No specific methods for the mitigation of effects of acute exposure to 1,4-dioxane were located other than measures to support vital functions. No information was located concerning mitigation of effects of lower-level or longer-term exposure to 1,4-dioxane. This, in part, may reflect the fact that no population has been identified as having been subjected or currently

undergoing exposure to excessive amounts of 1,4-dioxane. Attempts to propose studies of specific methods to reduce possible adverse effects do not appear warranted at this time.

Children's Susceptibility. There are no studies that specifically addressed exposure to 1,4-dioxane in children. Workers exposed to high amounts of 1,4-dioxane vapors experienced liver and kidney effects and some died (Barber 1934; Johnstone 1959). Volunteers exposed to low concentrations of 1,4-dioxane in the air experienced eye and nose irritation (Silverman et al. 1946; Yant et al. 1930; Young et al. 1977). It is reasonable to assume that children exposed in similar manners will experience similar effects. There is no information on whether the developmental process is altered in humans exposed to 1,4-dioxane. Very limited evidence with 1,4-dioxane in rats suggests that fetotoxicity may occur only at maternally toxic levels (Giavini et al. 1985), but further studies are necessary on this issue. The possibility that 1,4-dioxane may have endocrine-disrupting ability in mammals has not been systematically studied.

There are no data to evaluate whether pharmacokinetics of 1,4-dioxane in children are different from adults. There is no information on whether 1,4-dioxane can cross the placenta and there are no studies on whether 1,4-dioxane can be transferred from mother to offspring through maternal milk. Cross-fostering studies can provide important information regarding the role of *in utero* vs. lactation exposure to 1,4-dioxane in normal development. There are no data to permit an evaluation of whether metabolism of 1,4-dioxane is different in children than in adults.

Research into the development of sensitive and specific biomarkers of exposures and effects for 1,4-dioxane would be valuable for both adults and children. There are no data on the interactions of 1,4-dioxane with other chemicals in children. There are no pediatric-specific methods to reduce peak absorption 1,4-dioxane, to reduce body burdens, or to interfere with the mechanisms of action. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults, will also be applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies pertaining to 1,4-dioxane were identified in the FEDRIP (2004) database.

4. CHEMICAL AND PHYSICAL INFORMATION

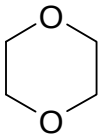
4.1 CHEMICAL IDENTITY

1,4-Dioxane or para-dioxane is also commonly referred as simply ‘dioxane’. However, 1,4-dioxane should not be confused with dioxin (or dioxins), which are a different class of chemical compounds. Information regarding the chemical identity of 1,4-dioxane is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

1,4-Dioxane is a colorless volatile liquid. 1,4-Dioxane is also completely miscible in water and organic solvents. The technical-grade product is >99.9% pure, but may contain bis(2-chloroethyl) ether as an impurity (DeRosa et al. 1996). Information regarding the physical and chemical properties of 1,4-dioxane is located in Table 4-2.

Table 4-1. Chemical Identity of 1,4-Dioxane

Characteristic	Information
Chemical name	1,4-Dioxane
Synonym(s)	1,4-diethylenedioxide; 1,4-dioxacyclohexane; 1,4-dioxanne (French); di(ethylene oxide); diethylene dioxide; diethylene ether; dioksan (Polish); diossano-1,4 (Italian); dioxaan-1,4 (Dutch); dioxan; dioxan-1,4 (German); dioxane; dioxane-1,4; dioxanne (French); dioxyethylene ether; glycol ethylene ether; para-dioxane; *p*-dioxan (Czech); *p*-dioxane; *p*-dioxin, tetrahydro-; tetrahydro-1,4-dioxin; tetrahydro-para-dioxin; tetrahydro-*p*-dioxin
Registered trade name(s)	No data
Chemical formula	$C_4H_8O_2$
Chemical structure	
Identification numbers:	
CAS Registry	123-91-1
NIOSH RTECS	JG8225000
EPA Hazardous Waste	U108; A toxic waste when a discarded commercial chemical product or manufacturing chemical intermediate or an off-specification commercial chemical product or a manufacturing chemical intermediate
OHM/TADS	No data
DOT/UN/NA/IMCO	UN 1165; IMO 3.2
HSDB	81
NCI	No data

CAS = Chemical Abstracts Services; CIS = Chemical Information System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of 1,4-Dioxane

Property	
Molecular weight (g/mol)	88.11[a]
Color	Clear[b]
Physical state	Liquid[a]
Melting point	11.8 °C[a]
Boiling point	101.1 °C[a]
Density	1.0329[a]
Odor	Faint pleasant odor[a]
Odor threshold:	
Water	No data
Air	24 ppm v/v[b]
Taste	No data
Solubility:	
Water	Miscible[c]
Other solvents	Soluble in organic solvents[a]
Partition coefficients:	
Log K_{ow}	-0.27[d]
Log K_{oc}	1.23[b]
Vapor pressure at 25 °C	38.1 mm Hg[e]
OH radical rate constant	1.09×10^{-11} cm^3/molecule-sec[f]
Henry's law constant at 25 °C	4.80×10^{-6} atm-cm^3/mole[g]
Autoignition temperature	356 °F (180 °C)[h]
Flashpoint	5–18 °C[a]
Flammability limits at 25 °C	Lower: 2.0%; Upper: 22%[b]
Incompatibilities	Strong oxidizers, decaborane, triethynyl aluminum[h]
Conversion factors (25 °C and 1 atm)	1 ppm = 3.6 mg/m^3; 1 mg/m^3 = 0.278 ppm[b]
Explosive limits	Vapor forms explosive mixtures with air over wide range[i]

[a]O'Neil et al. 2001
[b]EC 2002
[c]Riddick et al. 1986
[d]Hansch et al. 1995
[e]Daubert and Danner 1985
[f]Atkinson 1989
[g]Park et al. 1987
[h]NIOSH 2001
[i]National Fire Protection Association 1997

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

1,4-Dioxane is manufactured in a closed system by acid catalyzed conversion of diethylene glycol via dehydration and ring closure. The use of mono-, tri-, and polyethylene glycol and their ethers as raw materials have also been reported. Concentrated sulfuric acid (ca. 5 %) is used as the acid catalyst, although phosphoric acid, *p*-toluenesulfonic acid, strongly acidic ion-exchange resins, and zeolites are alternatives. Operating conditions vary; temperatures range from 130 to 200 °C and pressures range from a partial vacuum to slight pressure (i.e., 188–825 mm Hg). The ideal temperature is reported to be 160 °C. The reaction process is continuous and carried out in a heat vessel. The raw 1,4-dioxane product forms an azeotrope with water which is then vaporized from the reaction vessel by distillation. 1,4-Dioxane vapors are passed through an acid trap and two distillation columns to remove water and purify the product. Yields of ca. 90 % are achievable. 2-Methyl-1,3-dioxolane, 2-ethyl-1,3-dioxolane, and acetaldehyde are the main by-products. To a lesser extent, crotonaldehyde, and polyglycol are also formed during the production. The crude 1,4-dioxane is further cleaned by heating with acids, distillation (to remove glycol and acetaldehyde), salting out with NaCl, $CaCl_2$, or NaOH, and fine subsequent distillation (EC 2002; Surprenant 2002).

While the latter production process is the most important industrially, two other processes are especially useful for the production of substituted dioxanes. 1,4,-Dioxane can be prepared by ring closure of 2-chloro-2'-hydroxydiethyl ether (formed from ethylene glycol reacting with 1,2-dibromoethane) through heating with 20% sodium hydroxide, and by catalysed cyclo-dimerisation of ethylene oxide either over $NaHSO_4$, SiF_4, or BF_3, or at an elevated temperature with an acidic cation-exchange resin (EC 2002; Surprenant 2002).

Commercial production of 1,4-dioxane in the United States was first reported in 1951, but semi-commercial quantities were available in 1929 (NCI 1985). Currently, 1,4-dioxane is produced in the United States by two manufacturers; Dow Chemical (production site, Freeport, Texas) and Ferro Corporation (production site , Baton Rouge, Louisiana) (SRI 2003). Outside of the United States, 1,4-dioxane is produced by BASF AG in Lugwigshafen, Germany, Osaka Yuki and Toho Chem, Japan, and also in other countries around the world (ChemChannels 2004; EC 2002).

Recent information was not available on the production volumes of 1,4-dioxane in the United States. The total production of 1,4-dioxane for 1982 was estimated at 15 million pounds (6,800 metric tons), up from 12 million pounds (5,400 metric tons) reported in 1977 (HSDB 2004). The worldwide production capacity in 1985 was estimated to be 11,000–14,000 metric tons/year. In 1995, the production capacity of known producers and the worldwide production volume was estimated at 8,000 and 10,000 metric tons/year, respectively. In Europe, the production volume in 1997 was estimated to be 2,000–2,500 metric tons (EC 2002). However, current production levels of 1,4-dioxane are expected to be significantly less due to changing use patterns.

Table 5-1 lists the facilities in each state that manufacture or process 1,4-dioxane, the intended use, and the range of maximum amounts of 1,4-dioxane that are stored on-site. There are 43 facilities that produce or process 1,4-dioxane in the United States. The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 1995). This is not an exhaustive list (TRI02 2004).

5.2 IMPORT/EXPORT

No information was located on the current import/export levels of 1,4-dioxane for the United States. In 1977, at least $9.1x10^4$ kg of 1,4-dioxane was imported into the United States (HSDB 2004). However, current import levels of 1,4-dioxane are expected to be significantly less do to changing use patterns.

5.3 USE

Because of its broad range of solvent properties, 1,4-dioxane has found a variety of applications. 1,4-Dioxane is used as a solvent for chemical processing (e.g., adhesives, cleaning and detergent preparations, cosmetics, deodorant fumigants, emulsions and polishing compositions, fat, lacquers, pulping of wood, varnishes, waxes). 1,4-Dioxane has also been used as a laboratory reagent (e.g., mobile phase in chromatography); in plastic, rubber, insecticide, and herbicides; as a chemical intermediate; as part of a polymerization catalyst; and as an extraction medium of animal and vegetable oils. Other minor

Table 5-1. Facilities that Produce, Process, or Use 1,4-Dioxane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	100,000	999,999	6, 10
AR	2	1,000	999,999	10, 12
CA	2	1,000	9,999	7, 11
CO	1	1,000	9,999	10
GA	1	1,000	9,999	1, 5
IL	2	1,000	999,999	1, 4, 5, 12
LA	4	0	999,999	1, 4, 5, 12, 13
MN	1	1,000	9,999	10
MO	2	10,000	99,999	1, 5, 12, 13
MS	1	100	999	1, 5
NC	4	1,000	99,999	1, 5, 13
NE	1	10,000	99,999	12
NY	1	10,000	99,999	1, 5, 10
OH	1	10,000	99,999	12
OR	1	10,000	99,999	10
PR	1	10,000	99,999	10
SC	6	0	9,999	1, 5, 13, 14
TN	2	0	999	1, 5, 13
TX	3	0	999,999	1, 5, 6, 7, 12, 13
VA	1	1,000	9,999	10, 12
WI	1	100	999	1, 5, 13
WV	4	0	9,999	1, 5, 6, 12, 13, 14

Source: TRI02 2004 (Data are from 2002)

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

uses are in the manufacture of membrane filters, for measuring optical activity, and for cryoscopic determination. 1,4-Dioxane has been reported to be used in the production processes of the following product categories: pharmaceuticals/pesticides, magnetic tape, and adhesives. In the past, 1,4-dioxane was used primarily as a stabilizer in chlorinated solvents, particularity 1,1,1-trichloroethane. Approximately 90% of former production of 1,4-dioxane was used in this application. 1,4-Dioxane was typically used at a concentration of about 3.5% in chlorinated solvents. However, at the end of 1995, the use of 1,1,1-trichloroethane was limited under the Montreal Protocol due to the ozone depletion potential of 1,1,1-trichloroethane. Thus, current use of 1,4-dioxane as a stabilizer of 1,1,1-trichloroethane will not be significant (EC 2002; Hartung 1989; HSDB 2004; NICNAS 1998).

1,4-Dioxane has been found as an impurity in cosmetics, household and industrial detergents, and pharmaceuticals due to its occurrence as a by-product in ethoxylated emulsifiers (Hartung 1989). Currently, most manufacturers utilize vacuum stripping to remove 1,4-dioxane before formulation of ethoxylated surfactants in consumer cosmetics and household products (EC 2002).

5.4 DISPOSAL

The primary method of disposal of 1,4-dioxane is by incineration. Small amounts of 1,4-dioxane can be diluted with large amounts of water and subsequently discharged to waste water treatment plants (United Nations 1985). However, since 1,4-dioxane does not undergo significant biodegradation in waste water treatment plants, much of the 1,4-dioxane disposed by this method will end up in the environment. In contrast to biological or physical methods, chemical treatment has been found to be highly effective for the removal of 1,4-dioxane from water. 1,4-Dioxane is rapidly degraded by hydrogen peroxide in combination with a ferrous salt. Chlorination has also been found to be highly effective for the removal of 1,4-dioxane from water. For example, chlorine and hypochlorous acid are capable of oxidizing 1,4-dioxane (DOW Chemical Co. 1989). However, the extent to which 1,4-dioxane is removed from waste streams by these methods is unknown.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,4-Dioxane has been identified in at least 27 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for 1,4-dioxane is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 27 are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

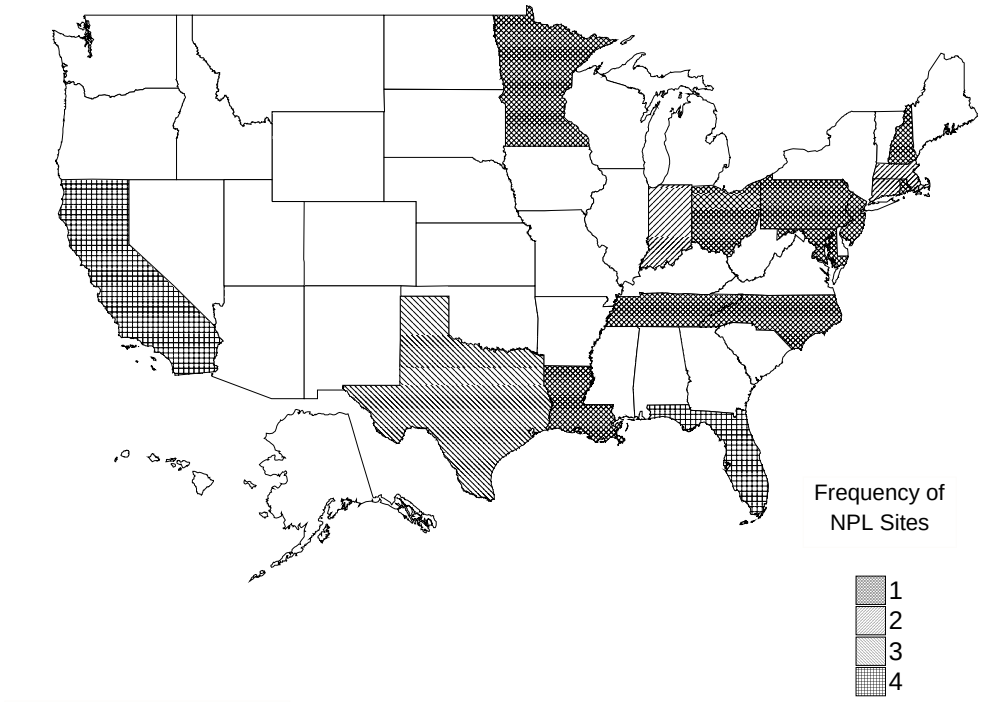
1,4-Dioxane is released into the environment during its production, the processing of other chemicals, its use, and with its unintentional formation during the manufacture of ethoxylated surfactants (EC 2002). In the past, 1,4-dioxane was released into the environment with its use as a stabilizer for 1,1,1-trichloro-ethane (TCA). Since the use of TCA has been discontinued, current releases from this source are expected to be very low.

1,4-Dioxane is expected to volatilize from the surfaces of water and soil. In air, it is subject to photooxidation with an estimated half-life of 1–3 days. 1,4-Dioxane does not undergo biodegradation in water and soils. It absorbs weakly to soil and will move quickly into groundwater. Bioconcentration, bioaccumulation, and biomagnification are not important for 1,4-dioxane.

Current levels of 1,4-dioxane in the environment are unavailable. Historical data (i.e., 1980s or earlier) suggest that ambient levels were 0.1–0.4 µg/m3 in air and 1 µg/L in water. Higher concentrations of 1,4-dioxane have been observed primarily in groundwaters.

The general population is exposed to negligible levels of 1,4-dioxane. The primary routes of human exposure to 1,4-dioxane are inhalation of 1,4-dioxane in air, ingestion of contaminated food and drinking water containing 1,4-dioxane, and dermal contact with contaminated consumer products (e.g., products containing ethoxylated surfactants). Because 1,4-dioxane may be found in tap water, human exposure to 1,4-dioxane may also occur during activities such showering, bathing, and laundering. Exposure to 1,4-dioxane in tap water through inhalation during showering or other indoor activities can result in

Figure 6-1. Frequency of NPL Sites with 1,4-Dioxane Contamination



higher exposures to 1,4-dioxane compared to ingestion of drinking water. Occupational exposure occurs during the production, processing, and use of 1,4-dioxane, which results in inhalation or dermal exposure.

6.2 RELEASES TO THE ENVIRONMENT

1,4-Dioxane is released into the environment during its production, processing, use, and with its unintentional formation during the manufacture of ethoxylated surfactants (EC 2002). In the past, 1,4-dioxane was release into the environment with its use as a stabilizer for TCA. Since the use of TCA has been discontinued, current releases from this source are expected to be very low.

1,4-Dioxane is unintentionally formed as an impurity during the manufacture of alkyl ether sulphates (AES) and other ethoxylated substances. However, much of the 1,4-dioxane impurity in these chemicals is removed through a stripping process during their manufacture. The stripper condensates from the manufacturing processes are discharged through normal plant effluents where they are diluted by other waste streams, and discharged as industrial wastes (NICNAS 1998). 1,4-Dioxane remaining as a by-product in end-use products (a large percentage of which may be used in domestic detergents and personal care products) will be released to publicly owned treatment works (POTWs) along with the surfactants, although this release will be far more diffuse.

According to the TRI, a total of 182,505 pounds (82,957 kg) of 1,4-dioxane were released to the environment in 2002. In addition, an estimated 964,136 pounds (307,877 kg) were transferred off-site, including to POTWs (TRI02 2004). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Since 1988, total on-site releases of 1,4-dioxane appear to be decreasing from a high of 1,234,968 pounds (560,173 kg) in 1993 to a low of 182,505 pounds (82,957 kg) in 2002.

6.2.1 Air

1,4-Dioxane may be released to air during its production, the processing of other chemicals (e.g., pharmaceuticals/pesticides), and its use (EC 2002). The total emissions of 1,4-dioxane from stationary sources in California are estimated to be at least 210,000 pounds per year, based on data reported under the Air Toxics “Hot Spots” Program (California ARB 1997).

No further information was located on the emissions of 1,4-dioxane to air.

The estimated release of 105,484 pounds (47,947 kg) of 1,4-dioxane to the atmosphere in 2002 accounted for about 57.8% of the estimated total on-site releases to the environment (TRI02 2004). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

1,4-Dioxane has been identified in air samples collected at 6 of the 1,647 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004). The maximum concentration was 1,476 µg/m^3.

6.2.2 Water

1,4-Dioxane may be released to surface water and groundwater during its production, the processing of other chemicals, its use, and with its unintentional formation during the manufacture of ethoxylated surfactants (EC 2002).

1,4-Dioxane was detected at 1 µg/L in effluents from the North Side and Calumet sewage treatment plants on the Lake Michigan Basin (Konasewich et al. 1978). 1,4-Dioxane has been observed in discharges into Lake Michigan near Chicago in 1977 (Konasewich et al. 1978) and in the Haw River in North Carolina (Dietrich et al. 1988). However, no information about the concentration of 1,4-dioxane or detection limit was provided in these sources.

Effluent of a sewage treatment plant discharging into the River Lee (United Kingdom) contained <1 ng/L in 8-hour mixed samples (EC 2002). Effluent of a sewage treatment plant from a polyethylene terephthalate (PET) manufacturing process contained 100 mg/L of 1,4-dioxane in 1995 (EC 2002).

In Kanagawa prefecture, Japan, Abe (1999) reported that 1,4-dioxane concentrations in effluents from chemical plants that used the compound as a solvent ranged from 0.4 to 4,020 µg/L, the combined collection treatments of apartment houses, and river basin sewage systems were 0.8–46, and 1.0–97 µg/L, respectively. No further data were located for emissions of 1,4-dioxane to water.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,4-Dioxane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	1,382	0	0	0	0	1,382	0	1,382
AR	2	5,516	0	0	0	0	5,516	0	5,516
CA	2	614	No data	0	0	0	614	0	614
CO	1	595	No data	0	0	0	595	0	595
GA	1	2,169	No data	0	0	0	2,169	0	2,169
IL	3	13,307	0	0	41	31	13,309	70	13,379
LA	4	3,834	14,658	0	3	0	18,492	3	18,495
MN	1	2,440	No data	0	0	0	2,440	0	2,440
MO	2	28	20	0	0	0	48	0	48
MS	1	619	5	0	0	0	624	0	624
NC	4	27,905	18,225	0	1,921	2	48,030	29	48,059
NE	1	6	No data	0	0	0	6	0	6
NY	1	1,183	2,700	0	0	2	3,883	2	3,885
OH	1	250	0	0	255	0	250	255	505
OR	1	104	No data	0	250	0	104	250	354
PR	1	1,700	No data	0	4	0	1,700	4	1,704
SC	9	19,798	17,766	14,711	2,341	0	37,564	17,052	54,616
TN	2	14,194	19,980	0	0	0	34,174	0	34,174
TX	3	7,470	783	946,471	0	0	8,253	946,471	954,724
VA	1	93	No data	0	0	0	93	0	93
WI	2	10	No data	0	0	0	10	0	10
WV	4	2,267	982	0	0	0	3,249	0	3,249
Total	48	105,484	75,119	961,182	4,815	35	182,505	964,136	1,146,641

Source: TRI02 2004 (Data are from 2002)

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

The estimated release of 75,119 pounds (34,145 kg) of 1,4-dioxane to surface water in 2002 accounted for about 41.2% of the estimated total on-site releases to the environment (TRI02 2004). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

1,4-Dioxane has been identified in surface water and groundwater samples, collected at 5 and 13 sites, respectively, of the 1,647 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004). The maximum concentrations were 14 µg/L in surface water and 730 µg/L in groundwater.

6.2.3 Soil

1,4-Dioxane may be released to soil during its production, the processing of other chemicals, its use, and with its unintentional formation during the manufacture of ethoxylated surfactants (EC 2002).

Between 1976 and 1985, Pall Life Sciences' (PLS) predecessor, Gelman Sciences in Ann Arbor, Michigan disposed of large quantities of waste water containing 1,4-dioxane on soil in a holding pond and through a waste injection well. 1,4-Dioxane was used as a solvent for cellulose acetate, a component of micro-porous filters. This chemical contaminated soil and rock layers and seeped into the groundwater. Disposal of this chemical in this way was stopped in 1986 (City of Ann Arbor 2003; MSU 2001). No further data were located for emissions of 1,4-dioxane to soil.

The estimated release of 4,815 pounds (2,189 kg) of 1,4-dioxane to land in 2002 accounted for about 2.7% of the estimated total on-site releases to the environment (TRI02 2004). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

1,4-Dioxane has been identified in soil samples, collected at 6 of the 1,647 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2004). Quantitative data are not available.

6.3 ENVIRONMENTAL FATE

1,4-Dioxane is expected to volatilize at a moderate rate from water and soil surfaces. In air, it is subject to photooxidation with an estimated half-life of 1–3 days. 1,4-Dioxane is relatively resistant to biodegradation in water and soils. It binds weakly to soils and will therefore move readily into groundwater. Bioconcentration, bioaccumulation, and biomagnification are not significant for 1,4-dioxane.

6.3.1 Transport and Partitioning

The Henry's law constant for 1,4-dioxane is $4.8x10^{-6}$ atm m^3/mole which indicates that 1,4-dioxane is expected to volatilize from water surfaces (Park et al. 1987; Thomas 1990). Based on this Henry's law constant, the volatilization half-life from a model river (1 m deep, flowing 1 m/second, wind velocity of 3 m/second) is estimated as 5 days. The volatilization half-life from a model lake (1 m deep, flowing 0.05 m/second, wind velocity of 0.5 m/sec) is estimated as 56 days (EPA 2000). The Henry's law constant for 1,4-dioxane also indicates that volatilization from moist soil surfaces may occur. The potential for volatilization of 1,4-dioxane from dry soil surfaces may exist based upon a vapor pressure of 38.1 mm Hg (Daubert and Danner 1985).

According to a classification scheme, an estimated K_{oc} value of 17 suggests that 1,4-dioxane is expected to have very high mobility in soil (Swann et al. 1983). This estimated K_{oc} value is calculated using a log K_{ow} of -0.27 and a regression-derived equation (Hansch et al. 1995; Thomas 1990). In the absence of significant degradation processes for 1,4-dioxane (see Section 6.3.2), 1,4-dioxane is susceptible to leaching from soil into groundwater In clay soils, 1,4-dioxane will not be adsorbed because of any specific interaction with the surface of clay minerals. However, 1,4-dioxane can get trapped in the interfacial region of clay soils due to its strong interaction with water molecules. This may result in a lower than expected mobility for 1,4-dioxane in clay soils (Zhang et al. 1990). Groundwater retardation factors (R_t) for 1,4-dioxane range from 1.0 to 1.6. These values indicate that 1,4-dioxane is expected to be a mobile compound (e.g., R_f for chloride=1.0, which is indicative of no retardation) in groundwater (Priddle and Jackson 1991).

According to a classification scheme, a bioconcentration factor (BCF) value of 3 for 1,4-dioxane suggests the potential for bioconcentration in aquatic organisms is low (Franke et al. 1994). This estimated BCF (the BCF is the concentration of the chemical in fish tissues over concentration of chemical in water) was

calculated using a log K_{ow} of -0.27 and a regression-derived equation (Hansch et al. 1995; Meylan et al. 1999). The results of an experimental bioconcentration study also reported very low BCF values (e.g., 0.2–0.7) for 1,4-dioxane (EC 2002). Therefore, bioconcentration, bioaccumulation, and biomagnification are unlikely to be significant for 1,4-dioxane.

6.3.2 Transformation and Degradation

6.3.2.1 Air

The primary loss mechanism for 1,4-dioxane in the atmosphere is photooxidation with OH radicals, while photolysis, reaction with ozone molecules, and reaction with nitrate radicals are insignificant in comparison (Grosjean 1990). The rate constant for OH radical photooxidation of 1,4-dioxane is $1.09x10^{-11}$ cm^3/molecule-sec (Atkinson 1989). Using OH radical concentrations of $0.5x10^6$–$1.5x10^6$ OH radicals/cm^3 and a 12-hour day, the atmospheric half-lives for 1,4-dioxane are 2.9 and 1.0 days, respectively. Reaction products from OH radical photooxidation are 2-oxodioxane (or c-$C_4H_7O_2$). The lifetime of this alkyl radical, 2-oxodioxane in air at 1 atm is 0.02 microsecond with respect to the addition of O_2 to give the corresponding peroxy radical (c-$C_4H_7O_2$)O_2. These radicals react rapidly ($t_{½}$=6 minutes based on NO concentration of $2.5x10^8$ molecules/cm^3) with NO to produce NO_2 and by inference (c-$C_4H_7O_2$)O alkoxy radicals. The sole atmospheric fate of this alkoxy radical is decomposition *via* C-C bond scission leading to the formation of ethylene glycol diformate (Platz et al. 1997). There are no known reactions for the *in situ* formation of 1,4-dioxane in the atmosphere (Grosjean 1990).

6.3.2.2 Water

Since 1,4-dioxane does not have functional groups that are susceptible to hydrolysis (Wolfe and Jeffers 2000), hydrolysis of 1,4-dioxane is not expected to occur in the environment. Since 1,4-dioxane does not adsorb light in the environmental spectrum (i.e., >290 nm), 1,4-dioxane is not expected to undergo direct photolysis in aqueous media. 1,4-Dioxane may undergo indirect photolysis by aqueous hydroxyl radicals near the water surface. The half-life for this reaction is 336 days at pH 7 (Anbar and Neta 1967). However, the extent of this reaction of OH radicals with 1,4-dioxane is unknown in the environment.

1,4-Dioxane has been found to be resistant to biodegradation (Alexander 1973; Dow Chemical Co. 1989; Fincher and Payne 1962; Heukelekian and Rand 1955; Mills and Stack 1954). Results of a biological oxygen demand (BOD) test for 1,4-dioxane indicate that negligible oxygen was consumed over a 20-day

test period (Swope and Kenna 1950). Mills and Stack (1954) noted that degradation of 1,4-dioxane was not observed in cultures of sewage microorganisms exposed for 1 year to waste water treatment plant effluents adjusted to contain 1,4-dioxane at concentrations ranging from 100 to 900 mg/L. In a different study, microorganisms present in either municipal or industrial activated sludge were unable to degrade 1,4-dioxane during 2 days of continuous exposure to concentrations ranging from 10 to 100 mg/L (Dow Chemical Co. 1989). Accordingly, it appears that 1,4-dioxane will not undergo significant degradation in conventional biological treatment systems. Thus, 1,4-dioxane has been classified as not readily biodegradable and it is not expected to rapidly biodegrade in the environment (Kawasaki 1980; Lyman et al. 1982).

Acclimated microbial cultures may be capable of degrading 1,4-dioxane under certain conditions. Roy et al. (1994) investigated the biodegradability of 1,4-dioxane in industrial wastes using microorganisms obtained from acclimated industrial waste. These authors found that pure 1,4-dioxane and industrial wastes containing 1,4-dioxane are biodegradable. Following a 10-day lag period, complete degradation of 150 mg/L of 1,4-dioxane was observed after 32 days of treatment using a electrolytic respirometer cell. However, partial degradation of 1,4-dioxane was observed at higher concentrations, which may resulted from the build up of intermediates inhibitory to the biodegradation process (Roy et al. 1994, 1995). Zenker et al. (2000) reported that a mixed microbial culture enriched from a 1,4-dioxane contaminated aquifer was capable of aerobically degrading 1,4-dioxane in the presence of tetrahydrofuran (THF). No biodegradation of 1,4-dioxane was observed in the absence of THF and the measured cell yield was similar during degradation of 1,4-dioxane with THF or with THF alone. This suggests that 1,4-dioxane was biodegraded via a co-metabolic process (i.e., transformation of a non-growth substance [1,4-dioxane] in the presence of a growth substrate [THF] or another transformable compound).

Zenker et al. (1999) reported that a mixed microbial culture enriched from a 1,4-dioxane contaminated soil was capable of aerobically degrading 1,4-dioxane in the presence of THF. 1,4-Dioxane and THF were added to the soil microcosm at a concentration of 200 mg/L under enhanced conditions, which included incubation at 35 °C and the addition of nitrogen, phosphorus, and trace minerals. Both 1,4-dioxane and THF were completely degraded within 100 days, while 1,4-dioxane alone degraded completely after 300 days of incubation. Microcosms incubated under ambient conditions exhibited no biodegradation of 1,4-dioxane or THF (Zenker et al. 1999).

Kelley et al. (2001) investigated the potential to enhance 1,4-dioxane biodegradation in both planted and unplanted soil, by adding the 1,4-dioxane-degrading actiomycte, *Amycolata sp*. CB1190. 1,4-Dioxane

was not removed within 120 days in sterile controls or in viable microcosms not amended with CB1190. Popular root extract (40 mg/L as chemical oxygen demand [COD]) stimulated 1,4-dioxane degradation in bioaugmented soil, and 100 mg/L of 1,4-dioxane was removed within 45 days. Other co-substrates that enhanced 1,4-dioxane degradation by CB1190 included THF and 1-butanol, while glucose and soil extract did not affect 1,4-dioxane degradation (Kelley et al. 2001). While long-term enrichments eventually yield cultures of CB1190 that are able capable of growth on 1,4-dioxane alone, THF appears to be the preferred growth substrate for CB1190 (Parales et al. 1994).

6.3.2.3 Sediment and Soil

No information was located on the transformation and degradation of 1,4-dioxane in soils and sediment. However, based on studies in aqueous systems, it is expected that 1,4-dioxane will be largely resistant to biodegradation in soils and sediments.

6.3.2.4 Other Media

Pure 1,4-dioxane is known to react with molecular oxygen at ambient temperatures to form peroxides and hydroperoxides in the course of long-term storage and handling (Howard and Ingold 1969). Peroxides are formed primarily with exposure to air and UV light. Formate esters are formed from subsequent transformations of peroxides and hydroperoxides by way of free-radical mechanisms (Jewett and Lawless 1980).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Recent information on the levels of 1,4-dioxane in the ambient environment are unavailable. Historical data (i.e., 1980s or earlier) suggest that ambient levels were 0.1–0.4 µg/m3 in air and 1 µg/L in water. Higher concentrations of 1,4-dioxane in groundwaters have been observed in aquifers contaminated with TCA.

6.4.1 Air

Recent information on the ambient levels of 1,4-dioxane in air is unavailable. Because the use of 1,4-dioxane has declined in recent years, current levels of 1,4-dioxane in the ambient air are likely to be less than levels reported in the 1980s or in earlier periods. In 1984, the concentration of 1,4-dioxane ranged from 0.1–0.4 μg/m^3 in ambient air sampled from the United States. No information was provided in this source on the locations where the air sampling occurred (EC 2002). In the early to mid 1980s, the mean ambient levels of 1,4-dioxane in indoor and outdoor air were measured as part of the VOC National Ambient Database in the United States (Shah and Singh 1988). The mean concentrations of 1,4-dioxane were 1.029 ppbv or 3.704 μg/m^3 (n=585; median, 0.000 ppbv) and 0.107 ppbv or 0.385 μg/m^3 (n=617; median, 0.000 ppbv) in indoor and outdoor air, respectively. 1,4-Dioxane was detected in outdoor air samples from the United States between 1981 and 1984 (detection limit unspecified). In the winter of 1984, 1,4-dioxane was detected in 67% of outdoor air samples from Los Angeles communities (n=25) at a median concentration of 0.27 μg/m^3. In the summer of 1984, 1,4-dioxane was detected in 22% of outdoor air samples from Los Angeles communities (n=23) at a median concentration of 0.02 μg/m^3. In the summer of 1984, 1,4-dioxane was detected in 20% of outdoor air samples from Antioch/West Pittsburg, California (n=10) at a median concentration of 0.03 μg/m^3 (Pellizzari et al. 1986). Between 1979 and 1984, the mean concentration of 1,4-dioxane in ambient air was 0.44 μg/m^3 (range, 0–30 μg/m^3; detected in 187 of 533 samples) in samples collected from 12 unspecified urban /suburban locations in the United States (EPA 1993).

In the summer of 1981 (July 6–August 16), the geometric mean concentrations of 1,4-dioxane in air near three industrialized urban areas (i.e., Newark, Elizabeth, and Camden, New Jersey) of the United States were 0.01 (21 of 38 samples positive), 0.02 (15 of 38 samples positive), and 0.005 μg/m^3 (21 of 35 samples positive), respectively (Harkov et al. 1983). The three same sites were also sampled from January 18–February 26, 1982. The geometric means of these samples ranged from 0 to 0.01 μg/m^3; 20% of samples were positive with a maximum value of 5.31 μg/m^3 (Harkov et al. 1984; EC 2002). Two ambient air samples taken in New Jersey were reported to contain 1,4-dioxane (Harkov et al. 1985). In 1983, near the Kramer Landfill in New Jersey, ambient air sampled contained 1,4-dioxane at a geometric mean concentration of 0.01 ppbv or 0.4 μg/m^3 (maximum, 0.09 ppbv or 0.3 μg/m^3). In 1982, at an urban/industrial site in Newark, New Jersey, ambient air contained 1,4-dioxane at a geometric mean concentration of 0.01 ppbv or 0.4 μg/m^3 (n=26; maximum, 1.45 ppbv or 5.22 μg/m^3). At various landfills in the United States, the concentration of 1,4-dioxane in landfill gas was reported to be 0.62 μg/m^3 and 0.33 g/m^3 (EC 2002).

In the early to mid 1980s, the mean ambient levels of 1,4-dioxane in indoor air were measured as part of the VOC National Ambient Database in the United States (Shah and Singh 1988). The mean concentration of 1,4-dioxane in indoor air was 1.029 ppbv or 3.704 µg/m^3 (n=585; median, 0.000 ppbv). 1,4-Dioxane was detected in indoor air samples from the United States between 1981 and 1984 (detection limit unspecified). In the winter of 1984, 1,4-dioxane was detected in 64% of indoor air samples from Los Angeles communities (n=25) at a median concentration of 0.26 µg/m^3. In the summer of 1984, 1,4-dioxane was detected in 17% of indoor air samples from Los Angeles communities (n=23) at a median concentration of 0.02 µg/m^3. In the summer of 1984, 1,4-dioxane was detected in 10% of indoor air samples from Antioch/West Pittsburg, California (n=10) at a median concentration of 0.07 µg/m^3 (Pellizzari et al. 1986). In a multi-national survey taken between 1978 and 1990, mean 1,4-dioxane levels were 11 µg/m^3 in indoor air samples taken from buildings (i.e., schools and offices) with unspecified complains (Brown et al. 1994). In June of 1990, 125 households in Woodland, California were monitored for a variety of toxic air contaminants. Approximately 21% of the indoor samples collected contained measurable amounts of 1,4-dioxane. The average concentration of 1,4-dioxane was below the quantifiable limit of 0.11 µg/m3, and the measurements ranged from below the quantifiable limit to 140 µg/m^3 (California ARB 1997).

6.4.2 Water

Recent information on the concentration levels of 1,4-dioxane in groundwater, surface water, and drinking water are limited. However, because the use of 1,4-dioxane has declined in recent years, current levels of 1,4-dioxane in the aqueous media are likely to be less than levels reported in the 1980s or in earlier periods.

In the 1970s, municipal water supplies in the United States were reported to contain 1 µg/L of 1,4-dioxane (Kraybill 1978); however, the frequency of this level was not provided. In a drinking water well in Massachusetts, a concentration of 2,100 µg/L was reported (Burmaster 1982). However, this well appears to be contaminated. In six drinking water wells (37% of samples) near a solid waste landfill located 60 miles southwest of Wilmington, Delaware, two wells were found to contain 0.1 and 0.5 µg/L 1,4-dioxane, but no 1,4-dioxane was detectable in the finished drinking water in the municipality using that well field (DeWalle and Chian 1981). Concentrations in private wells ranged from 0.001–1 to 200 mg/L (from 1–1,000 to 200,000 µg/L). The concentration of 1,4-dioxane in five wells near Circleville, Ohio ranged from <1 to 360 µg/L after contamination of groundwater following treatment of

industrial waste water (Hartung 1989). Drinking water from the Netherlands contained 1,4-dioxane at a concentration of 0.5 µg/L (EC 2002).

1,4-Dioxane was determined at 1.1–109 µg/L in contaminated groundwater in California (Draper et al. 2000). Extensive groundwater contamination (<0.01–220 mg/L or <10–220,000 µg/L) with more limited surface water contamination (<0.01–0.29 mg/L or <10–290 µg/L) resulted from treatment of industrial waste water in an unlined oxidation lagoon in Ann Arbor, Michigan (DeRosa et al. 1996). Current levels of 1,4-dioxane were about 1 µg/L in eight groundwater wells located in the vicinity of this site. However, the number of non-detects was not provided in this source (Michigan DEQ 2004). 1,4-Dioxane was discovered in groundwater at more than 250 ppm (mg/L) at a San Jose, California solvent recycling facility in 1998. In a survey of TCA release sites in California, it was found that 1,4-dioxane was present in a majority of these sites (concentrations unspecified) (Mohr 2004). At the Stanford Linear Accelerator Center (SLAC) in Menlo Park, California, the occurrence of 1,4-dioxane in groundwater is closely associated with TCA and its abiotic degradation product, 1,1-dichloroethane. It was found at this location at a maximum concentration of 7,300 ppb (Mohr 2004). Leachates from wells located near low level radioactive waste disposal sites contained 1,4-dioxane, but no quantitative date were presented (Francis et al. 1980). Between 1983 and 1986, 1,4-dioxane was detected in groundwater near three landfills in Canada at concentrations <1 µg/L (EC 2002). In groundwater beneath a landfill, the concentration of 1,4-dioxane was 500 µg/L at a site in Canada sampled in 1982 (EC 2002).

In 1982, 1,4-dioxane was detected in samples of river water from the Haw River in North Carolina, which flows through an industrialized section of the North Carolina Piedmont (Dietrich et al. 1988). However, no information on the levels of 1,4-dioxane in these samples were reported by the authors. 1,4-Dioxane at 1 µg/L was detected in the Chicago Sanitary and Ship Channel in the Lake Michigan basin (Konasewich et al. 1978). Surface water from the provincial area of Drente in the Netherlands contained 1,4-dioxane at concentrations ranging from 1 to 10 µg/L (EC 2002). At five different locations near the banks of the Rhine River in Germany, surface water contained <10 µg/L 1,4-dioxane in 1996 (EC 2002). River water collected from an unspecified river in the United Kingdom contained 1,4-dioxane, but no quantitative data were presented (Gelman Sciences 1989c). Dioxane concentrations in river water ranged from <0.024 to 0.69 µg/L in Kitakyushu, Japan (Kawata et al. 2003) and from 0.1 to 16 µg/L in Kanagawa, Japan (Abe 1999). The Japanese Ministry of the Environment reported that 1,4-dioxane in river and coastal waters ranged from <0.08 to 46 µg/L at 34–35 sites in Japan during fiscal year 1997–1999 (Kawata et al. 2003). 1,4-Dioxane was detected in surface water samples from 11 of 19 sites from Niigata, Japan at concentrations ranging from <0.03 to 0.39 µg/L (Kawata et al. 2003).

During the period of 1988–1991, the maximum concentration of 1,4-dioxane detected at Superfund sites in 21 states was 10 µg/L (Canter and Sabatinti 1994). 1,4-Dioxane ranged in concentration from 1.1 to 109 µg/L in leachate from hazardous waste disposal sites in Japan (Yasuhara et al. 1997). In 2000–2001, the concentration of 1,4-dioxane in leachate from a closed hazardous waste landfill in Japan ranged from 0.16 to 0.50 µg/L. At an open hazardous waste landfill, the concentration of 1,4-dioxane in leachate ranged from 0.91 to 10.6 µg/L (Yasuhara et al. 2003). At these landfills, waste plastics were disposed after either incineration, or crushing and pressing under heat. The heating process appears to have resulted in the formation of 1,4-dioxane, although a mechanism for this process was not provided (Yasuhara et al. 2003). The concentration of 1,4-dioxane in landfill leachates from eight hazardous disposal sites in Japan ranged from 1.100 to 109 µg/L (median, 3.900 µg/L) (Yasuhara et al. 1997). In May 1988, the concentration of 1,4-dioxane in an outwash aquifer near the Gloucester Hazardous Waste Landfill (Ottawa, Canada) ranged from ~300 to 2,000 µg/L with a 13% frequency of detection (detection limit=150 µg/L) (Lesage et al. 1990). The concentrations of 1,4-dioxane was reported to be 11, 8, and 36 µg/L in landfill leachates sampled from three municipal landfills in Göteburg, Sweden (Paxéus 2000).

In an industrial/urban area of Japan (i.e., Kanagawa prefecture), the concentration of 1,4-dioxane in river water ranged from 0.3 to 0.9 µg/L during the period of 1996–1998; and ranged from 0.2 to 0.4 µg/L in groundwater during the period of 1995–1997 (Abe 1999). High concentrations of 1,4-dioxane in polluted groundwater from this area ranged from <0.1 (not detected) to 52 µg/L and were correlated with TCA contamination of groundwater (Abe 1999). Romero et al. (1998) measured the concentration of 1,4-dioxane in industrial waste waters from producers of polyester resins in Barcelona, Spain. The polymer resins were polymerized using different glycols in acid catalyzed condensation reactions. In these waste water samples, 1,4-dioxane was detected at a mean concentration of 6,400 µg/L (range, <100–31,400 µg/L) and a frequency of 48.6% (Romero et al. 1998).

6.4.3 Sediment and Soil

No quantitative data were located on the concentrations of 1,4-dioxane in sediments or soil.

6.4.4 Other Environmental Media

There have been no systematic studies designed to determine the levels of 1,4-dioxane in foods. However, 1,4-dioxane has been detected in some foods, which may indicate that 1,4-dioxane may be a natural constituent. 1,4-Dioxane was found in chicken flavor and meat volatiles at unspecified concentrations (Shahidi et al. 1986). 1,4-Dioxane was also identified in volatile flavor compounds from fried chicken (Tang et al. 1983); however, no concentration levels were reported. Chung et al. (1983) identified 1,4-dioxane in the volatile components of tomato fruit juices and tomato fruit juices products by mass spectrometry, although levels of 1,4-dioxane were not quantified. 1,4-Dioxane was formed in trillnoloin (a component of fat oil used in deep-frying foods) after deep-fry heating (Chang et al. 1978). However, the concentration of 1,4-dioxane was not specified. Odor from cooked small shrimp was reported to contain 1,4-dioxane at unquantified levels (Choi et al. 1983). Sanceda et al. (1984) detected 1,4-dioxane in Patis, a Philippine fermented fish sauce, which is a commonly used food condiment in the diet of Southeast Asian people. It also may be readily available in some gourmet food stores in the United States. The concentration of 1,4-dioxane in patis was not specified. No further information on the detection of 1,4-dioxane in foods was located.

Food additives have been reported to contain 1,4-dioxane, although current levels were unavailable. For example, polysorbate 60 and polysorbate 80, which are used as food additives, have historically been found to contain 1,4-dioxane (Birkel et al. 1979). Polysorbate 60 and polysorbate 80 are produced from the polymerization of polyoxyethylene. Levels of 1,4-dioxane in these compounds have been reported to range from 4.8 to 6.0 ppm (mg/L) and from 5.3 to 5.8 ppm (mg/L), respectively. No further information on the levels of 1,4-dioxane in food additives was located.

In the FDA Cosmetic Handbook, it was reported that *cosmetics containing as ingredients ethoxylated surface active agents, i.e., detergents, foaming agents, emulsifiers, and certain solvents identifiable by the prefix, word or "PEG," "Polyethylene," "Polyethylene glycol," "Polyoxyethylene," "-eth-," or "-oxynol-," may be contaminated with 1,4-dioxane.* It is also reported that *it* (1,4-dioxane) *may be removed from ethoxylated compounds by means of vacuum stripping at the end of the polymerizations process without unreasonable increase in raw material cost* (FDA 1992).

Although manufacturers are able to remove 1,4-dioxane from ethoxylated raw materials by vacuum stripping, studies by FDA indicate that some ethoxylated raw materials may still contain 1,4-dioxane at significant levels. Since 1979, FDA has conducted periodic surveys of levels of 1,4-dioxane in

ethoxylated raw materials used in cosmetic products and finished cosmetic products (Black et al. 2001). In 1997, the average concentration of 1,4-dioxane in ethoxylated raw materials used in cosmetic products was 348 ppm (range, 45–1,102 ppm). In previous years, the average concentrations of 1,4-dioxane were 49 ppm (1979), 207 ppm (1980), 71 ppm (1993), and 180 ppm (1996). The average concentration of 1,4-dioxane in ethoxylated alkyl sulfate surfactants were reported to be 229 ppm (range, 71–580 ppm), 226 ppm (range, 6–1,410 ppm), 80 ppm (range, 16–243 ppm), 188 ppm (range, 20–653 ppm), and 348 ppm (range, 45–1,102 ppm) in the years 1979, 1980, 1983, 1993, 1996, and 1997, respectively (Black et al. 2001).

Although industry has taken steps to reduce 1,4-dioxane in ethoxylated surfactants, some cosmetic and household products may contain 1,4-dioxane at levels >10 ppm. For example, EPA (1992) examined 1,159 household products for chemical contaminants such as 1,4-dioxane. In one of six samples of laundry presoak spray analyzed, 1,4-dioxane was detected at a concentration of 15.0 w/w %. In an FDA survey of cosmetic finished products in the United States, the average concentrations of 1,4-dioxane were reported to be 50 ppm (range, 2–279 ppm), 19 ppm (range, 2–36 ppm), 2 ppm (range, 1–8 ppm) for the years 1981, 1982, and 1983, respectively (Black et al. 2001). After a 10-year break, FDA resumed its surveys of cosmetic finished products in 1992. A total of 99 products were analyzed for 1,4-dioxane between 1992 and 1997. In products analyzed since 1994, FDA focused on children's shampoos and bubble baths because children's products are typically formulated with ethoxylated raw materials. FDA observed that the downward trend in the levels of 1,4-dioxane previously observed in products analyzed in the late 1980s was no longer evident in the products analyzed in the 1990s. The average concentrations of 1,4-dioxane in cosmetic finished products were reported to be 41 ppm (range, 5–141 ppm), 79 ppm (range, 50–112 ppm), 45 ppm (range, 20–107 ppm), 74 ppm (range, 42–90 ppm), 14 ppm (range, 6–34 ppm), and 19 ppm (range, 6–34 ppm) in the years 1992, 1993, 1994, 1995, 1996, and 1997 (Black et al. 2001). These data suggest that not all raw materials producers are effectively controlling the levels of 1,4-dioxane, especially in children's products. Household laundry detergents, shampoos, soaps, skin cleansers were found to contain 1,4-dioxane at levels ranging from 6 to 160 ppm (Gelman Sciences 1989a, 1989b). In Denmark, cosmetic products and dishwashing detergent, which used polyethoxylated surfactants, contained 1,4-dioxane at levels ranging from 0.3 to 96 ppm and from 1.8 to 65 ppm, respectively (Rastogi 1990).

1,4-Dioxane has been reported to be a contaminant in other consumer products. For example, 1,4-dioxane was found to be an impurity in two household adhesive products from the United States at concentrations of 0.5 and 1–3% (NIH 2004). 1,4-Dioxane was detected in 2 of 62 samples of household

adhesives at concentrations of 1.0 w/w% for boot cement and 2.8 w/w% for universal cement (EPA 1992).

1,4-Dioxane is formed from the breakdown of ethylene glycol. In 1988, consumer anti-freeze products contained 1,4-dioxane at concentrations ranging from 100 to 3,400 ppb (Gelman Sciences 1989c). Radiator fluids have been found to contain slightly higher levels of 1,4-dioxane at concentrations ranging from 10 to 22,000 ppb (Gelman Sciences 1989c).

1,4-Dioxane was detected in 39 household aerosol products from Japan. In each of these samples, TCA was detected. The range of 1,4-dioxane concentration was 0.17–2.25% (Mori et al. 1992). A good correlation between the contents of 1,4-dioxane and TCA suggest that TCA containing 3% of 1,4-dioxane was used historically in the manufacture of aerosol products. However, because the use of TCA has been phased out in the United States since 1996, current levels of 1,4-dioxane in aerosol products should be limited.

Levels of 1,4-dioxane in human tissues and body fluids are not available for individuals from the United States. 1,4-Dioxane was identified but not quantified in human feces obtained from a healthy male individual from the former Soviet Union (Dmitriev et al. 1985). However, no information was provided in this study on the possible source of 1,4-dioxane in this feces sample or whether or not the individual was occupationally exposed to 1,4-dioxane.

Krotosznski et al. (1979) found 1,4-dioxane in the expired air of 24.8% of the samples taken from 54 normal humans. The geometric mean concentration was 0.253 µg/m^3. This concentration is significantly higher than those reported in the ambient air studies in New Jersey (see Section 6.4.1). However, no attempt was made to correlate the concentrations in the expired air with those found in the ambient air, nor was there an attempt to correlate these concentrations with life style or occupational exposures. Conkle et al. (1975) also found 1,4-dioxane (0.41 µg/hour) in the expired air of one out of eight volunteers. These authors speculated that 1,4-dioxane was a normal metabolic product, although neither this study nor the former monitoring study cited above had undertaken rigorous steps to prevent contamination with 1,4-dioxane during the analysis.

In 1989, 1,4-dioxane was detected in highway rest-stop radiator boil-over pools at concentrations ranging from <10 to 2,300 ppb (Gelman Sciences 1989a, 1989b).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The primary routes of human exposure to 1,4-dioxane for the general population are inhalation of 1,4-dioxane in air, ingestion of contaminated food and drinking water containing 1,4-dioxane, and dermal contact with consumer products. Because 1,4-dioxane may be found in tap water, human exposure to 1,4-dioxane may also occur during activities such showering, bathing, and laundering. Exposure to 1,4-dioxane in tap water through inhalation during showering or other indoor activities can result in higher exposures to 1,4-dioxane compared to ingestion of drinking water.

Recent levels of 1,4-dioxane in air are not available. In 1984, the concentration of 1,4-dioxane ranged from 0.1 to 0.4 μg/m^3 in ambient air sampled from the United States. Assuming that an adult breathes approximately 20 m^3 of air per day, the inhalation exposure would be 2–8 μg of 1,4-dioxane per day. Current exposure from air may likely be less that this value. This value may be somewhat higher for persons living near sources of 1,4-dioxane emission. Individuals employed at industrial facilities that produce, process, and use 1,4-dioxane will also have higher exposures. Similarly, 1,4-dioxane is taken into the body by ingestion of drinking water. Current levels of 1,4-dioxane in drinking water are not available. In the 1970s, drinking waters in the United States were reported to contain 1 μg/L of 1,4-dioxane (Kraybill 1978). Using this concentration and the consumption rate as 2 L/day, the 1,4-dioxane intake from drinking water would be 2 μg/day. Current exposure from drinking water may likely be less than this value. Recently, a Total Diet Study in Japan determined the intake of 1,4-dioxane in food based on the average intake of food in the Kanto area of Japan (Nishimura et al. 2004). The 1,4-dioxane content of 12 food groups ranged between 2 and 15 μg/kg. From these results, the total daily intake of 1,4-dioxane was calculated to be 0.440 μg. This study indicates that the amount of 1,4-dioxane intake contributed from food is very low. FDA has estimated the exposure to 1,4-dioxane from the use of polyethylene glycol mono-isotridecyl ether sulfate, sodium salt as a surfactant in adhesives intended for use in contact with food. Based on a daily diet of 3 kg, exposure to 1,4-dioxane has been estimated to be 0.2 ppb of daily diet or 0.6 μg/per person/per day (FDA 1998). Since most consumer products (e.g., detergents, shampoos, and cosmetic products) containing 1,4-dioxane may be diluted with water prior to application, dermal exposure is expected to be small in comparison to other exposures such as air, drinking water, and food.

Occupational exposure of individuals involved in the production, processing, or use of 1,4-dioxane may result from inhalation or dermal exposure (De Rosa et al. 1996). The National Occupational Exposure Survey (1981–1983) indicated that 86,489 individuals, including 30,542 women, potentially were

exposed to 1,4-dioxane (NIOSH 1977). This estimate was derived from observations of the actual use of the compound (25% of total observations) and the use of trade name products known to contain the compound (75%). The National Occupation Hazard Survey conducted by NIOSH from 1972 to 1974, estimated that 334,000 individuals were occupationally exposed to 1,4-dioxane, including 100,000 individuals occupationally exposed as a result of 1,4-dioxane used as a stabilizer in TCA (NIOSH 1976). In 1977, NIOSH estimated that 2,500 individuals were occupationally exposed to 1,4-dioxane, in addition to the 100,000 individuals occupationally exposed to both TCA and 1,4-dioxane (NIOSH 1977). OSHA reported that as many as 466,000 individuals may be occupationally exposed to 1,4-dioxane.

Individuals employed at chemical plants may be exposed to 1,4-dioxane as solvent vapors (Buffler et al. 1978). Between the period of 1994–1996, a survey in Hiroshima Prefecture, Japan was conducted to determine the levels of solvent vapors in 196 workplace areas. The survey was repeated every 6 months during this 3-year period. 1,4-Dioxane was reported in 6 of 1,176 cases at median and maximum concentrations of 0.5 and 0.8 ppm, respectively. 1,4-Dioxane was only detected in work areas where degreasing, cleaning, and wiping operations had occurred (Yasugi et al. 1998). During 1979, industrial hygiene monitoring was conducted at several plants which produced alcohol ethoxysulfate salts. Time-weighted-average concentrations of 1,4-dioxane in air samples collected for five different jobs and locations within these plants were at or below the detection limit of <0.1 ppm. A maximum TWA concentration of 0.4 ppm reported in this monitoring study (Shell Oil Co. 1988). 1,4-Dioxane and HEAA were detected in the urine of individuals occupationally exposed to 1,4-dioxane. Individuals were exposed to a time-weighted average concentration of 1.6 ppm 1,4-dioxane for 7.5 hours. The mean concentration of 1,4-dioxane and HEAA in urine samples from exposed individuals at the end of each workday were 3.5 and 414 µmol/L (0.31 and 36.5 mg/L), respectively (Young et al. 1976).

Individuals involved in the manufacture of ethoxylated chemicals may be exposed to 1,4-dioxane from its occurrence as a by-product, and in particular during the stripping process, which is carried out to remove 1,4-dioxane from certain ethoxylated chemicals (mainly surfactants and emulsifiers) (EC 2002). Because of the large quantities of TCA were previously used, past occupational exposure to 1,4-dioxane (used as a stabilizer) may have been significant, particularly in metal degreasing operations. As the manufacture of TCA is currently restricted, only limited exposure from this exposure source is expected to occur.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Specific information on the exposure of children to 1,4-dioxane does not exist. As for adults in the general population, small exposures occur from the normal ingestion of food and drinking water, inhaling air, and dermal contact with contaminated consumer products (e.g., containing ethoxylated surfactants). Home exposures may result from the unintentional consumption of consumer products (e.g., baby shampoo, household detergents) containing 1,4-dioxane. However, the extent of this possible exposure route in the general population is unknown.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who consume drinking water from contaminated wells may be exposed to higher levels of 1,4-dioxane. For example, groundwater has been reported to be contaminated with 1,4-dioxane in the following locations: Ann Arbor, Michigan; San Jose, California; and Menlo Park, California (DeRosa et al. 1996; Mohr 2004). The extent of 1,4-dioxane exposure for these populations is not known.

Individuals employed in occupations involved in the manufacture, processing, and handling and use of 1,4-dioxane will have potentially higher exposures to this chemicals. In addition, individuals involved in analytical science and research and development activities, which may utilize 1,4-dioxane as a solvent, may be exposed to higher levels of 1,4-dioxane.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,4-dioxane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,4-dioxane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Sufficient information about the chemical and physical properties (i.e., log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, etc.) of 1,4-dioxane are available to permit estimation of its environmental fate (see Table 4-2).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance and release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 2002, became available in July 2004. This database is updated yearly and should provide a list of industrial production facilities and emissions. Additional information is need on the sources of 1,4-dioxane contamination at contaminated sites.

1,4-Dioxane is currently produced in the United States, although current production volumes are not available. Information on current and future production levels of 1,4-dioxane are needed to determine whether the risk for human exposure to 1,4-dioxane is significant. Although, 1,4-dioxane is not widely used in the home, environment, or most workplaces, it can be present as a contaminant in materials that are found or used in these environments and, therefore, human exposures to 1,4-dioxane can occur. 1,4-Dioxane is used primarily as a solvent for chemical processing (e.g., adhesives, cleaning and

detergent preparations, cosmetics, deodorant fumigants, emulsions and polishing compositions, fat, lacquers, pulping of wood, varnishes, waxes). 1,4-Dioxane has also been reported to be used in the production processes of following product categories: pharmaceuticals/pesticides, magnetic tape, and adhesives. 1,4-Dioxane has been found as an impurity in cosmetics, household and industrial detergents, and pharmaceuticals due to its occurrence as a by-product in ethoxylated emulsifiers. 1,4-Dioxane may be present as a contaminant of food. However, no information is available that quantifies actual levels of 1,4-dioxane in food. Water is the most likely media to be contaminated with significant quantities of 1,4-dioxane (EC 2003; Hartung 1989).

Pure or nearly pure 1,4-dioxane is disposed of by incineration. It is expected that 1,4-dioxane is completely destroyed by this method. Aqueous solutions of 1,4-dioxane are disposed in waste water treatment facilities. Because 1,4-dioxane is resistant to biodegradation, complete mineralization of this chemical is not efficient. Thus, there may be need to develop effective methods of disposal for aqueous solutions of 1,4-dioxane. Additional information is needed on the amounts of 1,4-dioxane disposed of by each method.

Environmental Fate. 1,4-Dioxane is miscible in water and partitions primarily to the aqueous media in the environment. 1,4-Dioxane has high mobility in soil and has the potential to migrate into groundwater. In air, 1,4-dioxane will degrade by reaction with OH radicals with a half-life of 1–3 days (EPA 2000). 1,4-Dioxane has been found to be resistant to biodegradation in the environment (Alexander 1973; Dow Chemical Co. 1989; Fincher and Payne 1962; Heukelekian and Rand 1955; Mills and Stack 1954). 1,4-Dioxane is expected to persist in both water and soil.

Bioavailability from Environmental Media. 1,4-Dioxane is absorbed following inhalation, oral, and dermal contact (see Chapter 3). However, 1,4-dioxane is not bioconcentrated.

Food Chain Bioaccumulation. Because 1,4-dioxane is miscible in water, it is not bioconcentrated in plants, aquatic organisms, or animals. However, bioaccumulation in plants may occur by transpiration. 1,4-Dioxane is not biomagnified to any extent in prey organisms.

Exposure Levels in Environmental Media. 1,4-Dioxane has been detected in air, water, and foodstuff. Although historical data are available (e.g., 1980s and earlier), recent information on the levels of 1,4-dioxane in these media are not available. Reliable monitoring data for the levels of 1,4-dioxane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of

1,4-dioxane in the environment can be used in combination with the known body burden of 1,4-dioxane to access the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Estimates have been made for human intakes of 1,4-dioxane from air and drinking water. However, these estimates are based on historical monitoring data which may not be representative of current levels of 1,4-dioxane in environmental media. It is unclear how extensive the human exposure to 1,4-dioxane is indoors and from consumer products. Additional data that determines current levels of 1,4-dioxane in air, drinking water, food, and consumer products is necessary to assess human exposure to 1,4-dioxane.

Exposure Levels in Humans. 1,4-Dioxane has not been detected in the urine of individuals who are occupationally exposed to 1,4-dioxane (Young et al. 1976). Two studies conducted by Conkle et al. (1975) and Krotosznski et al. (1979) involving 54 and 8 volunteers, respectively, detected 1,4-dioxane in a small number of expired air samples collected from these volunteers, but the source of the measured 1,4-dioxane could not be determined because the studies did not adequately document lifestyle or occupation. No other biological monitoring studies have been done in populations surrounding hazardous waste sites or in the general population. This information is necessary for assessing the need to conduct health studies on these populations. No estimates have been made for human intake of 1,4-dioxane from various environmental media. This information is necessary for determining the routes of exposure to 1,4-dioxane from these various media.

Exposures of Children. Children are exposed to 1,4-dioxane in the same manner as adults. Exposure and body burden studies on children would be useful. Children who take frequent bubble baths may be exposed to higher levels of 1,4-dioxane than adults due to possible contamination of ethoxylated surfactants found in these commercial products. Additional studies are needed to determined whether this is a significant exposure route for children. It is not known whether children are different in their weight-adjusted intake of 1,4-dioxane. Additional studies would help to determine if children are more or less exposed to 1,4-dioxane compared to adults. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for 1,4-dioxane were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates

the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

Historically, 1,4-dioxane has been used as a stabilizer in TCA at concentrations up to 4%. Often 1,4-dioxane is present at sites where TCA has been found as a contaminant. TCA is currently one of the compounds for which a Subregistry has been established in the Volatile Organic Compounds (VOCs) Registry. The VOCs Registry is part of the National Exposure Registry (NER), which was created and is being maintained by the Agency for Toxic Substances and Disease Registry.

6.8.2 Ongoing Studies

No ongoing studies were located as a result of a search of the Federal Research in Progress (FEDRIP 2004) database.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,4-dioxane, its metabolites, and other biomarkers of exposure and effect to 1,4-dioxane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

Levels of 1,4-dioxane in environmental and biological samples are determined analytically by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID). The determination of 1,4-dioxane at parts-per-billion (ppb or µg/L) concentrations in samples where water is present (e.g., water, soil, sediment, and tissues) is difficult. This is because of the high solubility of 1,4-dioxane in water. As a polar volatile organic compound (VOC), 1,4-dioxane has a low purge efficiency from water compared to non-polar VOCs. Consequently, 1,4-dioxane has a poor purge-and-trap GC-MS response. The purge-and-trap technique also suffers from interferences by some substances. 1,4-Dioxane gives poor response with headspace sample introduction due to its low volatility from water. The partition coefficients for 1,4-dioxane lead to low recoveries in single contact liquid-liquid extraction (LLE), and very large solvent-to-water ratios are needed to achieve acceptable recoveries (Draper et al. 2000). Because of these limitations, alternative techniques have been developed to improve the determination of 1,4-dioxane. Methods have been developed to extract 1,4-dioxane extracted from the aqueous phase using solid phase extraction (SPE) followed by desorption with an organic solvent, heated purge-and-trap with salting out, azeotropic distillation; and continuous LLE. Isotopic dilution has also been used to correct for variability in MS instrument response.

7.1 BIOLOGICAL MATERIALS

Methods for the specific analysis of 1,4-dioxane and its metabolites in biological tissues and fluids are limited. Since the human body rapidly metabolizes 1,4-dioxane to 1,4-dioxane-2-one and HEAA, the metabolites of 1,4-dioxane may be used as biomarkers of exposure to 1,4-dioxane (Young et al. 1976).

Using heated headspace technique, 1,4-dioxane was determined in blood or urine (e.g., 4–5 mg) by heating a sample in a sealed tube to 120 °C. Volatiles from this sample were then analyzed by gas chromatography with the limit of detection being 0.01–0.02 µg (Royal Society of Chemistry 1988).

Groves et al. (1997) described the analysis of organic vapors in exhaled breath, which could provide information about occupational exposures to 1,4-dioxane. Analysis was conducted using an array of four polymer-coated surface-acoustic-wave (SAW) sensors and an adsorbant preconcentrator for rapid breath analysis. The adsorbant used in the preconcentrator was a porous styrene-divinylbenzene resin. Limits of detection range from 3.7 to 10.2 µg/L for 1,4-dioxane.

Biomarkers of exposure to 1,4-dioxane are the urinary metabolites, 1,4-dioxane-2-one and HEAA (Royal Society of Chemistry 1988). Young et al. (1976) described a method for detection of 1,4-dioxane and HEAA in urine. Urine samples were treated with hydrochloric acid/methanol to convert HEAA to its methyl ester. Samples were then directly injected into a GC-MS for simultaneous analysis of 1,4-dioxane and HEAA. The detection limits were 0.07 and 0.1 µg/mL, respectively.

Analytical methods for the determination of 1,4-dioxane and its metabolites in biological samples are given in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

NIOSH 1602 is used to determine the concentration of 1,4-dioxane in a 10-L air sample by GC-FID. Samples are collected by drawing air through a solid sorbent tube containing coconut shell charcoal. The flow rate is between 0.01 and 0.2 L/minute for a total sample size of 0.5–15 L. 1,4-Dioxane is eluted from the solid sorbent with agitation using carbon disulfide. The carbon disulfide eluent sample is then injected directly into the GC-FID. Detection limits are 0.01 mg per sample (NIOSH 1994).

Table 7-1. Analytical Methods for Determining 1,4-Dioxane in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood or urine	Heat sample in a sealed tube to 120 °C; inject headspace into GC	GC	0.01–0.02 µg	No data	Royal Society of Chemistry 1988
Exhaled breath	Pre-concentrate on breath sample on porous styrene-divinylbenzene resin	Four polymer-coated surface-acoustic-wave (SAW) sensors	3.7–10.2 µg/L	No data	Groves et al. 1997
Urine	Samples treated with HCl/methanol to convert HEAA to its methyl ester; samples then directly injected into GC-MS	GC-MS	0.07 µg/mL (1,4-dioxane); and 0.1 µg/mL (HEAA)	No data	Young et al. 1976

GC = gas chromatography; HCl = hydrochloric acid; HEAA = β-hydroxyethoxyacetic acid; MS = mass spectrometry

EPA Method 8015B is used to determine the concentration of 1,4-dioxane in environmental samples by GC. Samples may be introduced into the GC by direct injection (e g., aqueous samples) including the concentration of analytes by azeotropic distillation (EPA Method 5031). Purge-and-trap and solvent extraction are not appropriate for this method. Detection of the analyte is achieved by using a FID. Method detection limits for 1,4-dioxane in water, groundwater, and leachate are 12, 15, and 16 µg/L, respectively. Method detection limits for 1,4-dioxane in solids (e.g., incinerator ash and kaolin) are 0.31 and 0.16 mg/kg, respectively. Using azeotropic microdistillation, recoveries for 1,4-dioxane in groundwater, leachate, incinerator ash, and kaolin were 96–124, 102–103, 48–106, and 48–105%, respectively (EPA 1996a).

EPA Method 8260B is used to determine 1,4-dioxane in a variety of solid waste matrices by GC. This method is applicable to nearly all types of samples, regardless of water content, including various air sampling trapping media, groundwater and surface water, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments. Samples may be introduced to the capillary GC column by direct injection following dilution, sample concentration by azeotropic distillation (EPA Method 5031), and closed system vacuum distillation (EPA Method 5032) for aqueous, soil, oil, and tissue samples. Detection of the analyte eluted from the capillary column is achieved by using MS. The estimated quantitation limit for 1,4-dioxane is somewhat instrument dependent and also dependant on the choice of sample preparation/introduction method. No information on the recoveries for 1,4-dioxane were provided for this method (EPA 1996b).

EPA Method 1624 is used to determine 1,4-dioxane in water and in municipal and industrial discharges by isotopic dilution GC-MS. In this method, isotopically labeled 1,4-dioxane-d_8 is added to the sample as an isotope dilution standard. The samples are then introduced into the GC using a purge-and-trap methodology. 1,4-Dioxane is separated by GC and detected by MS. The labeled compounds serve to correct for the variability of the analytical technique. The detection limit for this method is 10 µg/L (EPA 2001).

Draper et al. (2000) described a sensitive method for detection of 1,4-dioxane in drinking water. This method was based on continuous LLE of 1,4-dioxane from aqueous samples by dichloromethane. Extraction of 1,4-dioxane in dichloromethane was followed by analysis using GC-MS. Detection limits as low as 0.2 µg/L were achieved in this method.

Epstein et al. (1987) described two methods for the determination of 1,4-dioxane in water and in solids and sediments. In the first method, 1,4-dioxane is extracted from water and soil samples using a heated purge-and-trap system following salting out with sodium sulfate at 1.6 M. GC-MS is then used as the method of analysis. The detection limit reported for this method was 2 ppb with recoveries averaging 85%. In the second method, 1,4-dioxane is adsorbed on coconut shell charcoal followed by desorption with carbon disulfide/methanol. Analysis of the desorbate is conducted by GC with flame ionization detection. The limit of quantitation is around 2 ppb with recoveries ranging from 63 to 129%.

Kadokami et al. (1990) described a method for analysis of 1,4-dioxane in water by GC-MS. Preconcentration of 1,4-dioxane is achieved by passing the aqueous sample through an activated carbon column followed by elution with acetone-dichloromethane. The organic extract is then concentrated with a Kuderna-Danish concentrator followed by direct injection into the GC-MS with a selective ion monitor. The method detection limit was reported to be 0.024 µg/L. Recoveries of 1,4-dioxane from organic-free water, seawater, and river water were 98–101, 102, and 101%, respectively. Kawata et al. (2001) described a similar method of analysis for 1,4-dioxane in water. However, in this method, the solid-phase extraction media was activated carbon fiber felt with acetone as the elution media. Analytical determination of 1,4-dioxane was accomplished by GC-MS detection. The method detection limit was reported to be 0.03 µg/L. Recoveries of 1,4-dioxane in groundwater and river water were 97 and 92%, respectively.

Analytical methods for the determination of 1,4-dioxane in environmental samples are given in Table 7-2.

7.3 OTHER SAMPLES

Several methods are available that may be used to determine 1,4-dioxane in food, consumer cosmetic products, and surfactant raw materials.

The concentration of 1,4-dioxane in food additives may be determined using the 1,4-dioxane limit test (Committee on Food Chemicals Codex 1996). 1,4-Dioxane is extracted from a sample placed in a closed-system vacuum distillation apparatus. The distillate is then analyzed using GC-FID. The detection limit was not specified for this method. Daniels et al. (1981) utilized a similar methodology in the analysis of

Table 7-2. Analytical Methods for Determining 1,4-Dioxane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Samples collected by drawing air through a solid sorbent tube containing coconut shell charcoal; 1,4-dioxane eluted with agitation using carbon disulfide	GC-FID	0.01 mg per sample	No data	NIOSH 1994 (NIOSH Method 1602)
Drinking water	Continuous liquid-liquid extraction using dichloromethane	GC-MS	0.2 µg/L	No data	Draper et al. 2000
Water, seawater, and river water	Pre-concentration by passing aqueous sample through an activated carbon column followed by elution with acetone-dichloromethane; organic extract concentrated with a Kuderna-Danish concentrator	GC-MS with a selective ion monitor	0.024 µg/L	98–102%	Kadokami et al. 1990
Groundwater and river water	Solid-phase extraction using activated carbon fiber felt with acetone as eluent	GC-MS	0.03 µg/L	97%, 92%	Kawata et al. 2001
Water, groundwater, leachate	Direct injection or azeotropic distillation (i.e., EPA Method 5031)	GC-FID	12–16 µg/L	96–124% (ground-water), 102–103% (leachate)	EPA 1996a (EPA Method 8015B)
Water, and municipal and industrial discharges	Isotopically labeled 1,4-dioxane-d_8 is added to the sample as an isotope dilution standard	Purge-and-trap GC-MS	10 µg/L	No data	EPA 2001 (EPA Method 1624)
Water, and solids and sediments	Adsorbed on coconut shell charcoal followed by desorption with carbon disulfide/methanol	GC-FID	2 ppb (µg/L or µg/kg)	63–129%	Epstein et al. 1987
Water, and solids and sediments	Extracted from water and soil samples using a heated purge-and-trap system following salting out with sodium sulfate at 1.6 M	GC-MS	2 ppb (µg/L or µg/kg)	85%	Epstein et al. 1987

Table 7-2. Analytical Methods for Determining 1,4-Dioxane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater and surface water, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments	Azeotropic distillation (i.e., EPA Method 5031) or closed system vacuum distillation (i.e., EPA Method 5032)	GC-MS	No data	No data	EPA 1996b (EPA Method 8260B)

1,4-Dioxane-d_8 = deuterium labeled 1,4-dioxane (or $C_4D_8O_2$); EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; kg = 10^3 grams; L = liter; mg = 10^{-3} grams; µg = 10^{-6} grams; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; ppb = parts per billion

1,4-dioxane in the food additive, polysorbate 65. The detection limit was not specified. Recoveries for 1,4-dioxane concentrations ranging from 0.5 to 600 ppm were from 85 to 101%, respectively.

Stafford et al. (1980) described the determination of 1,4-dioxane in ethoxylated surfactants using a direct injection GC method. 1,4-Dioxane is extracted from the ethoxylated surfactants using chlorobenzene, which is then diluted, and injected directly into the GC-FID. The detection limit was reported to be 0.5 mg/kg with a recovery of approximately 100%. Rastogi (1990) reported method for the identification and quantification of 1,4-dioxane in polyethoxylated surfactants using headspace GC-MS. Dichloromethane and 1,4-dioxane-d_8 are added to the surfactant sample in a closed vial, which is then heated at 80 °C for 16–18 hours. The headspace gases are sampled with a gas-tight syringe and injected into the GC-MS for quantitative analysis. The detection limit for this method was approximately 0.3 ppm with recoveries of 92–94%.

1,4-Dioxane may be quantified in commercial cosmetic products by reversed-phase high-performance liquid chromatography (Scalia et al. 1990). Cosmetic samples are extracted using solid-phase extraction cartridges. Samples are then analyzed directly on a reverse-phase column with spectrophotometric detection at 200 nm and acetonitrile-water as eluent. The limit of detection was reported to be 6.5 µg/g. The recovery of 1,4-dioxane was between 81.5 and 90.1% in the 30–90 µg/g range. Ghassempour et al. (1998) described a modified GC-MS method for determination of 1,4-dioxane in cosmetic products (i.e., polyoxyethylene compound). Cosmetic product samples are prepared by dissolution of the material in dichloromethane. Samples are then analyzed directly by injection into a programmable temperature vaporizer attached to GC-MS. The minimum detection limit was reported to be 1 ng/L for this method. However, as this value is very low, the detection limit is likely much higher than reported by the authors.

Analytical methods for the determination of 1,4-dioxane in food and food additives, cosmetics, and ethoxylated surfactant samples are given in Table 7-3.

7.4 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,4-dioxane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research

designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,4-dioxane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.4.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Existing methods do not appear to be sensitive enough to measure background levels of 1,4-dioxane and its metabolite, HEAA, in the population (Young et al. 1976). Standard methods for the determination of 1,4-dioxane and its metabolite, HEAA are needed to determine whether the general population is exposed to 1,4-dioxane.

Effect. Existing methods appear to be sensitive enough to measure levels of 1,4-dioxane and its metabolite, HEAA, at levels at which biological effects may occur in humans (Young et al. 1976). However, more precise, accurate, and reliable methods would be useful to determine levels of biological effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The purpose of analytical methods is to identify contaminated areas and to determine if contaminant levels constitute a concern for human health. The media that are of most concern for human exposure to 1,4-dioxane are drinking water, food, and cosmetic products. In water, there are methods sensitive enough to measure background levels in the environment down to the sub-ppb level (<1 µg/L) (Draper et al. 2000; Kadokami et al. 1990; Kawata et al. 2001). Standard methods are also available for measurement of 1,4-dioxane in air and water samples (EPA 1996a, 1996b; NIOSH 1994). Methods have also been reported for the determination of 1,4-dioxane in food and food additives (Committee on Food Chemicals Codex 1996; Daniels et al. 1981), cosmetics (Ghassempour et al. 1998; Scalia et al. 1990), and ethoxylated surfactant materials (Rastogi 1990; Stafford et al. 1980). Additional or improved methods

that offer increased sensitivity would be useful for determining sub-ppb (<1 µg/L) levels of 1,4-dioxane in foods and food additives, which would be helpful in determining whether exposure to 1,4-dioxane in food is significant for the general population.

7.4.2 Ongoing Studies

The Environmental Health Laboratory Science Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of 1,4-dioxane and other volatile organic compounds in blood. These methods use purge-and-trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

No ongoing studies on 1,4-dioxane were found as a result of a search of the Federal Research in Progress (FEDRIP 2004).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding 1,4-dioxane in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an acute-duration inhalation MRL of 2 ppm for 1,4-dioxane based on a LOAEL of 50 ppm for eye irritation in humans (Young et al. 1977). No NOAEL was defined in the study. An uncertainty factor of 30 was used (3 for using a minimal LOAEL and 10 to protect sensitive populations).

ATSDR has derived a chronic-duration inhalation MRL of 1 ppm for 1,4-dioxane based on a NOAEL of 111 ppm for liver effects in rats (Torkelson et al. 1974). No LOAEL was defined in the study. The MRL was derived using the PBPK model developed by Reitz et al. (1990). An uncertainty factor 30 was used (3 for using dosimetric adjustments and 10 to protect sensitive populations). The chronic-duration inhalation MRL of 1 ppm also has been adopted as the intermediate-duration inhalation MRL.

ATSDR has derived an acute-duration oral MRL of 4 mg/kg/day for 1,4-dioxane based on a NOAEL of 370 mg/kg/day for nasal effects in male rats (JBRC 1998a). The LOAEL was 1,010 mg/kg/day in males and 1,040 mg/kg/day in females. An uncertainty factor of 100 was used (10 for the protection of sensitive populations and 10 for animal to human extrapolation).

ATSDR has derived an intermediate-duration oral MRL of 0.6 mg/kg/day for 1,4-dioxane based on a NOAEL of 60 mg 1,4-dioxane/kg/day for liver effects in male rats (JBRC 1998b). The LOAEL was 150 mg/kg/day in males and 200 mg/kg/day in females. An uncertainty factor of 100 was used (10 for the protection of sensitive populations and 10 for animal to human extrapolation).

ATSDR has derived a chronic-duration oral MRL of 0.1 mg/kg/day for 1,4-dioxane based on a NOAEL of 9.6 mg 1,4-dioxane/kg/day for liver effects in male rats (Kociba et al. 1974). The LOAEL was 94 mg/kg/day in males and 148 mg/kg/day in females. An uncertainty factor of 100 was used (10 for the protection of sensitive populations and 10 for animal to human extrapolation).

Table 8-1. Regulations and Guidelines Applicable to 1,4-Dioxane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B[a]	IARC 1999
WHO	No data		
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	20 ppm[b]	ACGIH 2003
NIOSH	REL (30-minute ceiling TWA)	1 ppm[c]	NIOSH 2004
	IDLH	500 ppm	
EPA	Hazardous air pollutant		EPA 2004d 42USC7412
OSHA	PEL (8-hour TWA) for general industry	100 ppm[b]	OSHA 2004c 29CFR1910.1000, Table Z-1
	PEL (8-hour TWA) for construction industry	100 ppm[b]	OSHA 2004b 29CFR1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry	100 ppm[b]	OSHA 2004a 29CFR1915.1000, Table Z
b. Water			
EPA	Drinking water standards and health advisories		EPA 2004b
	1-Day HA for a 10-kg child	4.0 mg/L	
	10-Day HA for a 10-kg child	0.4 mg/L	
	10^{-4} cancer risk	0.3 mg/L	
c. Food			
FDA	Indirect food additive for use only as a component of adhesives		FDA 2003 21CFR175.105
d. Other			
ACGIH	Carcinogenicity classification	Group A3[d]	ACGIH 2003
EPA	Carcinogenicity classification	B2[e]	IRIS 2004
	RfC	No data	
	RfD	No data	
	Oral slope factor	1.1×10^{-2} $(mg/kg/day)^{-1}$	
	Drinking water unit risk	3.1×10^{-7} $(\mu g/L)^{-1}$	
	Community right-to-know; release reporting; effective date	01/01/1987	EPA 2004e 40CFR372.65
	Designated as a hazardous substance pursuant to Section 112 of the Clean Air Act and Section 3001 of RCRA		EPA 2004a 40CFR302.4
	Reportable quantity	100 pounds	

Table 8-1. Regulations and Guidelines Applicable to 1,4-Dioxane

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Hazardous waste identification	U108	EPA 2004c 40CFR261, Appendix VIII
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2002
STATE			
a. Air			
No data			
b. Water			
	Drinking water guidelines		HSDB 2004
Florida		5 µg/L	
Maine		70 µg/L	
Massachusetts		50 µg/L	
Michigan		3 µg/L	
North Carolina		7 µg/L	
c. Food			
No data			
d. Other			
No data			

[a]Group 2B: Possibly carcinogenic to humans.
[b]Skin designation: Potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, or of probable greater significance, by direct skin contact with the substance.
[c]Potential occupational carcinogen.
[d]Group A3: Confirmed animal carcinogen with unknown relevance to humans.
[e]B2: probable human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = Health Advisory; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; RfC = reference concentration; RfD = reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

The EPA (IRIS 2004) has not derived a reference dose (RfD) or a reference concentration (RfC) for 1,4-dioxane, but derived an oral slope actor of $1.1x10^{-2}$ $(mg/kg/day)^{-1}$ based on the increased incidence of nasal tumors in male Osborne-Mendel rats (NCI 1978). As part of its systematic prioritization process, the EPA is currently re-evaluating the health assessment for 1,4-dioxane (EPA 2004f).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD**10** would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration(Lo) (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(Lo) (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose(50) (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose(50) (TD50)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm

Reference: Young JD, Braun WH, Rampy LW. 1977. Pharmacokinetics of 1,4-dioxane in humans. J Toxicol Environ Health 3:507-520.

Experimental design: The acute-duration inhalation MRL is based on a LOAEL of 50 ppm for eye irritation in humans in a study with volunteers. In that study, the effects of 50 ppm 1,4-dioxane vapors were evaluated in four healthy male volunteers. Prior to the study, the subjects provided a complete history and underwent tests including chest x-ray, EKG, respiratory function tests, a conventional battery of 12 blood chemistry tests plus triglyceride and creatinine determinations, and complete hematological and urine analyses. Except for the chest x-ray, the tests were repeated 24 hours and 2 weeks after the exposure. The exposure was carried out in a 26.7 m^3 chamber under dynamic airflow conditions.

Effects noted in study and corresponding doses: The tests conducted 24 hours and 2 weeks after exposure did not reveal any exposure-related abnormalities. Eye irritation was a frequent and the only complaint throughout the exposure, but no data were provided in the study. Tolerance to the odor of 1,4-dioxane occurred during exposure. Two of the subjects could not perceive the odor after 4 and 5 hours in the chamber. The LOAEL of 50 ppm was divided by an uncertainty factor of 30 (3 for a minimal LOAEL and 10 to protect sensitive populations) to derive the MRL. Because the effects observed were local irritation effects, they were not time-dependent, an adjustment to 24-hour exposure was not necessary.

Dose and end point used for MRL derivation: 50 ppm; LOAEL for eye irritation in humans.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[ ] for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? NA.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: Other studies with volunteers support the finding of Young et al. (1977). For example, Silverman et al. (1946) exposed

12 subject to various concentrations of 1,4-dioxane for only 15 minutes and determined a NOAEL of 200 ppm for eye and nose irritation; the LOAEL was 300 ppm. Wirth and Klimmer (1936) reported that slight mucous membrane irritation started to take place in volunteers at exposure concentrations about 278 ppm for a few minutes (unspecified) and that at 1,390 ppm for several minutes, the subjects described prickling in the nose and scratchiness and dryness in the throat. Fairley et al. (1934) reported a NOAEL of 2,000 ppm (only level tested) for respiratory and ocular effects in six subjects exposed to 1,4-dioxane for only 3 minutes. Finally, Yant et al. (1930) described slight eye, nose, and throat irritation in a group of five subjects exposed to 1,600 ppm (only level tested) 1,4-dioxane for only 10 minutes. The available studies in animals used exposure concentrations much higher than the one tested by Young et al. (1977) that often caused death among the animals.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 20
Species: rat

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

Reference: Torkelson R, Leong BKJ, Kociba RJ, et al. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol Appl Pharmacol 30:287-298.

Although there were no adequate intermediate-duration inhalation studies in humans or animals from which to derive an intermediate-duration inhalation MRL, the chronic-duration inhalation MRL of 1 ppm was adopted also for intermediate-duration exposure. The intermediate-duration database for 1,4-dioxane consists of one early study that reports the effects of 1,4-dioxane in several animal species exposed to high doses (lethal in some cases) of 1,4-dioxane (Fairley et al. 1934). Rats, mice, guinea pigs, and rabbits were exposed 3 hours/day, 5 days/week for periods of up to 12 weeks. At termination, examination of the animals revealed moderate to severe liver and kidney toxicity occurring at all exposure levels in all of the species tested. The lowest exposure level was 1,000 ppm.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 20
Species: rat

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

Reference: Torkelson R, Leong BKJ, Kociba RJ, et al. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol Appl Pharmacol 30:287-298.

Experimental design: The chronic-duration inhalation MRL is based on a NOAEL of 111 ppm for liver effects in rats and application of the physiologically-based pharmacokinetic (PBPK) model of Reitz et al. (1990). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were provided by Dr. Richard Reitz. A detailed description of the model and its application is presented in Appendix B. In the Torkelson et al. (1974) study, groups of Wistar rats (288/sex) were exposed to 1,4-dioxane vapors at a concentration of 0.4 mg/L (111 ppm) 7 hours/day, 5 days/week for 2 years. Controls were exposed to filtered room air. End points examined included clinical signs, eye and nasal irritation, skin condition, respiratory distress, and tumor formation. Hematological parameters (hemoglobin, red blood cell count, total and differential leukocyte counts, corpuscular volume) were determined after 16 and 23 months of exposure. Blood collected at termination was used also for determination of clinical chemistry parameters (serum ALT and alkaline phosphatase activity, BUN, total protein). Liver, kidneys, and spleen were weighed and the major tissues and organs were processed for microscopic examination.

Effects noted in study and corresponding doses: Exposure to 1,4-dioxane vapors had no significant effect on mortality, or body weight gain and induced no signs of eye or nasal irritation or respiratory distress. Slight but statistically significant changes in hematological and clinical chemistry parameters were within the normal physiological limits and were considered of no toxicological importance. Organ weights were not significantly affected. Microscopic examination of organs and tissues did not reveal treatment-related effects. It should be noted that because no significant effects were seen at the concentration tested, the true study NOAEL is probably higher than 111 ppm. Using the Reitz et al. (1990) model for interspecies extrapolation of 1,4-dioxane dosimetry for data from the Torkelson et al. (1974) study yields a human equivalent NOAEL of 35.5 ppm. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) yields a chronic-duration inhalation MRL of 1 ppm. Using EPA's standard methodology for extrarespiratory effects for a category 3 gas rather than the PBPK model, and an uncertainty factor of 30, results in an MRL of 2 ppm for 1,4-dioxane. The derivation using the PBPK model is preferred because it yields a more protective MRL.

Dose and end point used for MRL derivation: 111 ppm; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustments
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? NA

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The exposure concentration was not duration-adjusted.

Other additional studies or pertinent information which lend support to this MRL: The limited human data support the chronic-duration inhalation MRL. An occupational study by Thiess et al. (1976) provided no evidence of ill effects in a group of 74 German workers exposed to concentrations ranging from 0.006 to 14.3 ppm for an average of 25 years. In another epidemiological study, mortality rates were evaluated among workers exposed to 0.1–17 ppm 1,4-dioxane for up to 21 years (Buffler et al. 1978). No differences were found between observed and expected incidences of cancer.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: rat

Minimal Risk Level: 4 [X] mg/kg/day [ ] ppm

Reference: JBRC. 1998a. Two-week studies of 1,4-dioxane in F344 and BDF1 mice (drinking water studies). Kanagawa, Japan: Japan Bioassay Research Center.

Experimental design: The acute-duration oral MRL is based on a NOAEL of 370 mg 1,4-dioxane/kg/day for nasal effects in rats. In that study, F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 1,110, 3,330, 10,000, 30,000, or 90,000 ppm for 2 weeks (0, 130, 370, 1,010, or 2,960 mg/kg/day for males; 0, 160, 400, 1,040, or 2,750 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body weight, gross necropsy and histopathology on 2–4 animals per group.

Effects noted in study and corresponding doses: All animals in the 90,000 ppm group died. Two females in the 30,000 ppm (2,750 mg/kg/day) died. Body weight gain was reduced by about 25% in males and females from the 30,000 ppm groups (2,960 mg/kg/day for males, 2,750 mg/kg/day for females). Food and water consumption was reduced approximately by 30% in males and females from the 30,000 ppm group. At 30,000 ppm (2,960 mg/kg/day for males; 2,750 mg/kg/day for females), there was nuclear enlargement of the olfactory epithelium, swelling and vacuolar changes of the central area in the liver, hydropic change of the proximal renal tubule, and vacuolar changes in the brain. At 10,000 ppm, there was nuclear enlargement of the olfactory epithelium (1,010 mg/kg/day in males; 1,040 mg/kg/day in females). The study NOAEL was 400 mg/kg/day in females and 370 mg/kg/day in males (3,330 ppm). Therefore, the dose level of 370 mg/kg/day in male rats is used as the basis for the MRL. The MRL was calculated by dividing the male NOAEL of 370 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations). It should be pointed out that the study has several limitations, including the lack of statistical analysis of the results, only a small number (2–3) of animals were examined, and end points such as hematology, clinical chemistry, clinical signs, and gross examinations were not conducted or reported. Although these limitations compromise the study, the findings are consistent with what is known about target organs for 1,4-dioxane.

Dose and end point used for MRL derivation: 370 mg/kg/day; NOAEL for nasal effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? The conversion was done by the investigators, and the doses listed are means of ranges provided by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: JBRC (1998a) conducted a similar study in male and female Crj:BDF_1 mice and identified NOAELs of 1,380 and 1,780 mg/kg/day for liver effects in males and females, respectively. Doses of 2,550 and 3,220 mg/kg/day caused swelling of the central area of the liver in males and females, respectively. No nasal effects were observed in the mice. Most of the rest of the acute database consists of high-dose early studies aimed at determining LD_{50} values (de Navasquez 1935; Kesten et al. 1939; Laug et al. 1939; Pozzani et al. 1959; Smyth et al. 1941). The lowest dose that caused lethality was 327 mg 1,4-dioxane/kg/day in a study that tested only three dogs (Schrenk and Yant 1936). This dose was provided in the drinking water and killed one dog after 10 days of treatment. Doses of 375 mg/kg/day killed another dog in 9 days. However, because the dogs were allowed to drink the 1,4-dioxane solution only twice daily during a limited period of time, dehydration may have played a role in their death. A gestational exposure study in rats identified a maternal and developmental NOAEL and LOAEL of 513 and 1,033 mg/kg/day, respectively (Giavini et al. 1985).

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: rat

Minimal Risk Level: 0.6 [X] mg/kg/day [ ] ppm

Reference: JBRC. 1998b. Thirteen-week studies of 1,4-dioxane in F344 and BDF1 mice (drinking water studies). Kanagawa, Japan: Japan Bioassay Research Center.

Experimental design: The intermediate-duration oral MRL is based on a NOAEL of 60 mg 1,4-dioxane/kg/day for nasal and liver effects in rats. In that study, groups of F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 640, 1,600, 4,000, 10,000, or 25,000 ppm for 13 weeks (0, 60, 150, 330, 760, or 1,900 mg/kg/day in males; 0, 100, 200, 430, 870, 2,020 mg/kg/day in females). End points evaluated included clinical signs, food and water consumption, body weight, complete hematology and clinical chemistry tests, urinalysis, organ weights, gross necropsy and histopathology. No information was provided as to when the blood and urine samples were collected.

Effects noted in study and corresponding doses: One female in the 25,000 ppm (2,010 mg/kg/day) died. Body weight gain was reduced at 870 and 2,020 mg/kg/day in females and 1,900 mg/kg/day in males. Food consumption was reduced 13% in females at 2,020 mg/kg/day. Water consumption was reduced in a dose-related manner in all male groups and in females at ≥200 mg/kg/day. Hematology test showed significant increases in erythrocyte counts, hemoglobin, hematocrit, and neutrophils, and a decrease in lymphocytes in males at 1,900 mg/kg/day, and decreases in mean corpuscular volume and platelets in females at 2,020 mg/kg/day. Total protein and albumin were decreased in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and leucine aminopeptidase (LAP) activities, and levels of cholesterol, triglycerides, sodium, and glucose were significantly elevated in high dose males and females. Urinary pH was decreased in males at ≥330 mg/kg/day and in females at ≥870 mg/kg/day. Absolute and relative kidney weights were increased in females at ≥200 mg/kg/day. Nuclear enlargement of the respiratory epithelium occurred in males at ≥150 mg/kg/day and in females at ≥200 mg/kg/day; nuclear enlargement of the olfactory and tracheal epithelium occurred in males at ≥330 mg/kg/day and in females at ≥430 mg/kg/day. Swelling of the central area of the liver was observed in males at ≥150 mg/kg/day and in females at ≥870 mg/kg/day, and vacuolar changes in the liver occurred in males at ≥760 mg/kg/day and in females at 2,020 mg/kg/day. Nuclear enlargement of the proximal tubule of the kidneys was seen in males at ≥760 mg/kg/day and in females at ≥870 mg/kg/day. Hydropic changes in the proximal tubule of the kidneys and vacuolar changes in the brain occurred in high-dose males and females (1,900 and 2,020 mg/kg/day, respectively). The study LOAEL was 150 mg/kg/day for liver and nasal effects in male rats. To derive the MRL, the NOAEL of 60 mg/kg/day for liver effects in males was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for sensitive populations), yielding an intermediate-duration oral MRL of 0.6 mg/kg/day. Limitations of the study include lack of reporting on clinical signs and gross necropsy.

Dose and end point used for MRL derivation: 60 mg/k/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? The conversion was done by the investigators, and the doses listed are means of ranges provided by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: A study by Lundberg et al. 1987) supports the liver findings of JBRC (1998b). The study used male Sprague-Dawley rats (8–11/group) that were treated with 100 or 1,000 mg 1,4-dioxane/kg by gavage in saline 5 days/week for 7 weeks. One week after the last treatment, the rats were killed and the livers were processed for microscopic examination. The livers of high-dose rats showed enlarged foamy hepatocytes mainly in midzonal regions. The foamy appearance was due to vacuoles shown to contain fat. No treatment-related histopathological alterations were observed in the liver at the 100 mg/kg/day dose level.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: September 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 39
Species: rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Kociba RJ, McCollister SB, Park C, et al. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol Appl Pharmacol 30:275-286.

Experimental design: Groups of Sherman rats (60/sex/dose level) were treated with 1,4-dioxane in the drinking water at levels of 0 (controls), 0.01, 0.1, or 1% for 716 days. Based on body weight and water consumption data, the investigators estimated that the water provided doses of 1,4-dioxane of 0, 9.6, 94, and 1,015 mg/kg/day for males and 0, 19, 148, and 1,599 mg/kg/day for females. Blood samples were collected from controls and high-dose rats during the 4th, 6th, 12th, and 18th months of the study and at termination. Additional end points evaluated included clinical signs, body weight, organ weights, and gross and microscopic examination of major tissues and organs.

Effects noted in study and corresponding doses: Treatment with 1,4-dioxane significantly increased mortality in high-dose males and females beginning at about 2–4 months of treatment. These rats showed degenerative changes in both the liver and kidneys. Body weight gain was significantly reduced in high-dose animals from the beginning of the study. Microscopic lesions were restricted to the liver and kidneys from the mid- and high-dose groups. The liver lesions consisted of various degrees of hepatocellular degeneration and necrosis and evidence of hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation. The NOAEL for liver effects was 9.6 mg/kg/day in males and 19 mg/kg/day in females. The LOAELs were 94 mg/kg/day in males and 148 mg/kg/day in females. The kidneys showed tubular epithelial degeneration and necrosis, and there was evidence of renal tubular regeneration as indicated by increased tubular epithelial regenerative activity. There were no compound-related alterations in hematological parameters at any time point. The MRL of 0.1 mg/kg/day was calculated by dividing the male rat NOAEL of 9.6 mg/kg/day by an uncertainty factor of 100 (10 to protect sensitive populations and 10 for animal to human extrapolation). The carcinogenic effects were limited to the liver and nasal turbinates from high-dose animals.

Dose and end point used for MRL derivation: 9.6 mg/k/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? A conversion was done by the investigators.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information which lend support to this MRL: The NOAEL and LOAEL for liver effects from Kociba et al. (1974) are supported by the results of JBRC (1998c). In that study, groups of Fischer 344/DuCrj rats (50/sex/dose level) received 1,4-dioxane in the drinking water for 104 weeks. 1,4-Dioxane was administered at levels of 0, 200, 1,000, and 5,000 ppm for 2 years (0, 16, 81, and 398 mg/kg/day for males; 0, 21, 103, and 514 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body and organ weights, comprehensive hematology and clinical chemistry tests, urinalysis, and gross and microscopic examination of major organs and tissues. In males, relative liver weight was increased at ≥81 mg/kg/day and absolute liver weight was increased at 398 mg/kg/day. A significant increase incidence of spongiosis, hyperplasia, and clear and mixed cell foci was observed in the liver from male rats with ≥81 mg 1,4-dioxane/kg/day, but not 16 mg/kg/day. These lesions were observed in females dosed with 514 mg/kg/day, but not with lower doses. In addition, in this study, female rats dosed with ≥103 mg 1,4-dioxane/kg/day showed nuclear enlargement of the olfactory epithelium of the nasal cavity; no such lesions occurred with the lower female rat dose of 21 mg/kg/day.

The NCI (1978) bioassay in Osborne-Mendel rats used somewhat higher dose levels than Kociba et al. (1974) and JBRC (1998c), but did not observe liver lesions in male rats dosed with 240 mg 1,4-dioxane/kg/day, a dose level that caused liver hyperplasia in male Fischer 344 rats dosed with 81 mg/kg/day or that caused hepatocyte degeneration in Sherman rats dosed with 94 mg/kg/day. Since the dosing method was the same in the three studies, the drinking water, the different results may reflect differences in strain sensitivity.

An alternate approach to derive a chronic-duration oral MRL is to use the PBPK model developed by Reitz et al. (1990), as was done for the chronic inhalation data. Using the model, it can be estimated that the human equivalent dose to the NOAEL of 9.6 mg/kg/day for liver effects in males is 12.9 mg/kg/day. Applying an uncertainty factor of 30 (3 for using dosimetric adjustments and 10 for sensitive populations) to the human NOAEL of 12.9 mg/kg/day yields a chronic-duration oral MRL of 0.4 mg/kg/day, which supports the MRL of 0.1 mg/kg/day derived above. A detailed explanation of the use of the model is presented in Appendix B.

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX B. USE OF PBPK MODEL FOR INTERSPECIES EXTRAPOLATION OF 1,4-DIOXANE DOSIMETRY

Interspecies extrapolation (rat-to-human) of 1,4-dioxane dosimetry was achieved using PBPK models described in Reitz et al. (1990). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were provided by Dr. Richard Reitz. Parameter values used in the interspecies extrapolation are presented in Table B-1. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Reitz et al. (1990) (results shown in Figures B-1 and B-2).

Two internal dose metrics (DM) were simulated:

(1) The time-integrated 1,4-dioxane concentration in liver (DM1):

$$DM1 = AUCL = \left(\int_0^t \frac{dAL}{dt} \right) \cdot \frac{1}{VL}$$

where AUCL is area under1,4-dioxane liver concentration-time, AL is the amount (mg) of 1,4-dioxane in liver, and VL is the volume of the liver (L).

(2) Daily average time-integrated 1,4-dioxane concentration in liver (DM2):

$$DM2 = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hoursrs) and N_d is the number of days in the simulation.

Note that DM2 is the time-averaged value of DM1, with an averaging time of 24 hours. The steady-state value of DM2 fluctuates (periodically) during an intermittent exposure (i.e., 7 hours/day, 5 days/week), whereas the value of DM1 increases over time, with the *rate of increase* fluctuating periodically, once a steady state is reached. If the simulated exposure duration is held constant, both DM1 and DM2 produce nearly identical inter-species external dose extrapolations. This was confirmed in the current analysis. Although DM2 was reported in Reitz et al. (1990), the results reported here are for DM1 (Table B-2), which can be more readily duplicated for a given exact exposure duration (i.e., there is no periodicity in DM1).

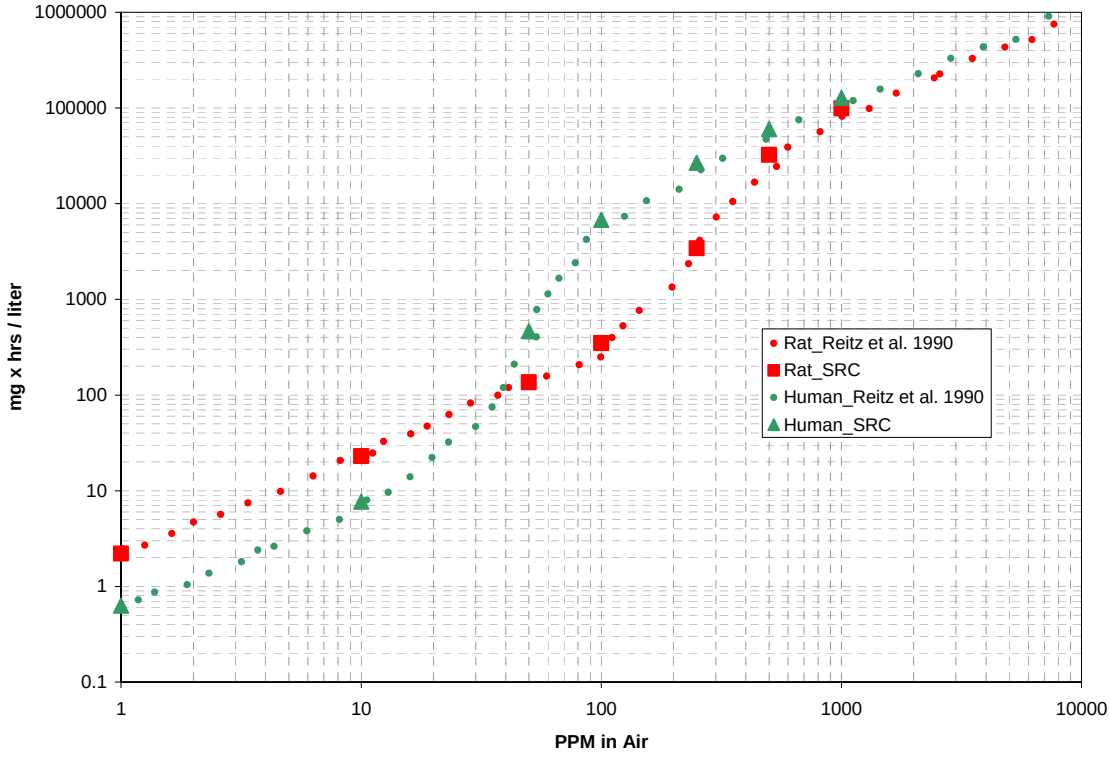
Exposures in the Torkelson et al. (1974) rat inhalation study were simulated as exposures of a 0.4-kg rat to 111 ppm (400 mg/m^3), 7 hours/day (7 hours/24 hours), 5 days/week (120 hours/168 hours) for 2 years (17,420 hours). The predicted value for DM1 corresponding to this exposure was 53,079 mg-hour/L (row 1 of Table B-2). Human equivalent exposure concentrations (HEC) were simulated as exposures of a 70-kg human for 24 hours/day, 7 days/week for 2 years. The human model was run iteratively, varying the external exposure concentration until the model converged on the value for DM1 for the rat. The HEC that corresponded to a value of DM1 of 53,079 mg-hour/L was 35.5 ppm (128 mg/m^3, row 2, Table B-2).

Table B-1. Parameters Values for Rat and Human 1,4-Dioxane Models[a]

Parameter	Definition	Rat model	Human model
BW	Body weight (kg)	0.4	70
VLC	Liver volume (fraction of body)	0.04	0.031
VFC	Fat volume (fraction of body)	0.05	0.231
VSC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.037
VRC	Slowly-perfused tissue volume (fraction of body)	0.70	0.561
VB	Blood volume (fraction of body)	0.05	0.05
QCC	Cardiac output (L/hour-kg body weight)	15.0	30.0
QPC	Alveolar ventilation rate (L/hour-kg body weight)	15.0	30.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.25
QFC	Fat blood flow (fraction of cardiac output)	0.05	0.05
QSC	Rapidly-perfused blood flow (fraction of cardiac output)	0.52	0.52
QRC	Slowly-perfused blood flow (fraction of cardiac output)	0.18	0.18
PB	Blood:air partition coefficient	1,850	3,660
PL	Liver:air partition coefficient	1,557	1,557
PF	Fat:air partition coefficient	851	851
PS	Rapidly-perfused:air partition coefficient	1,557	1,557
PR	Slowly-perfused:air partition coefficient	1,557	1,557
VMAXC	Maximum rate of metabolism (mg/hour-kg body weight)	13.7	6.35
KM	Michaelis-Menten coefficient for metabolism (mg/L)	29.4	3.0
KA	Rate constant for gastrointestinal absorption ($hour^{-1}$)	5.0	5.0
KME	Rate constant for elimination of metabolites ($hour^{-1}$)	0.28	0.56

[a]Reitz et al. (1990)

Figure B-1. Comparison of Model Output Reported in Reitz et al. (1990, Figure 5a) and from SRC Version of the Reitz et al. (1990) 1,4-Dioxane Model (Inhalation)

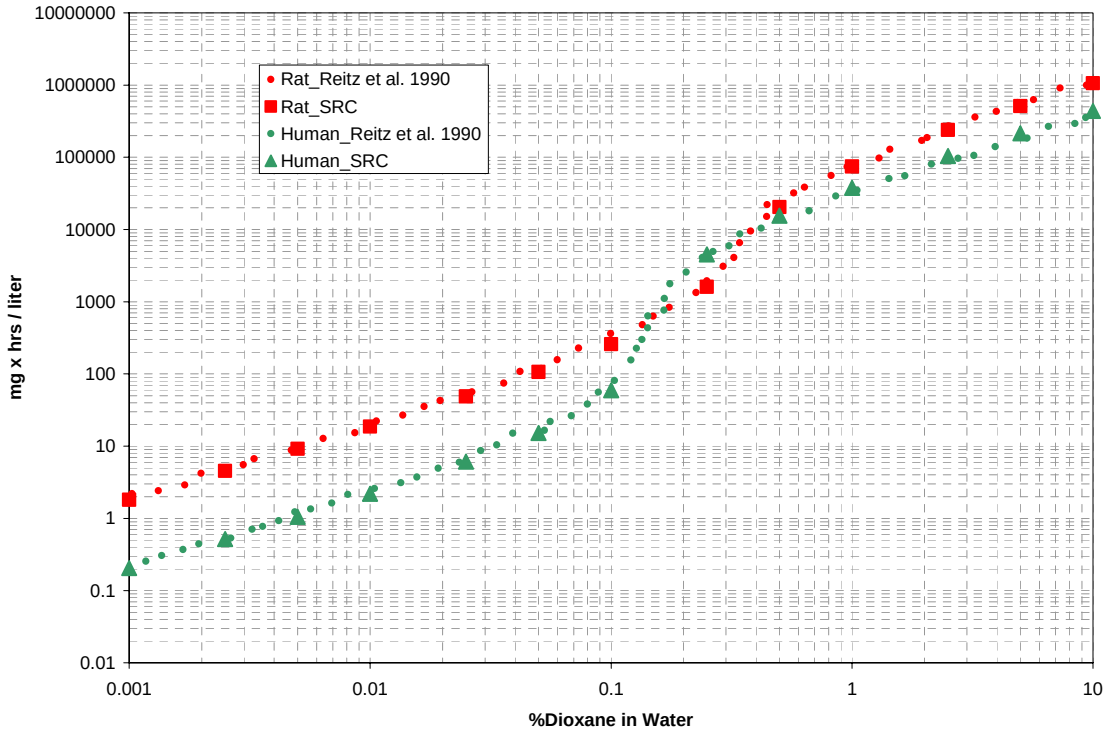


Simulations are of the average daily area under concentration–time curve for 1,4-dioxane in liver, for a 2-year (17,520 hours) continuous inhalation exposure (AAUCL, mg-hours/L)

$$AAUCL = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hours) and N_d is the number of days in the simulation. Simulations are of a 0.4-kg rat and 70-kg human.

Figure B-2. Comparison of Model Output Reported in Reitz et al. (1990, Figure 5a) and from SRC Version of the Reitz et al. (1990) 1,4-Dioxane Model (Oral)



Simulations are of the average daily area under concentration–time curve for 1,4-dioxane in liver, for a 2-year (17,520 hours) continuous exposure to 1,4-dioxane in drinking water (AAUCL, mg-hours/L)

$$AAUCL = \frac{\Sigma AUCL_{i...n}}{N_d}$$

where $AUCL_i$ is the area under the concentration time curve for a single day (24 hours) and N_d is the number of days in the simulation. Simulations are of a 0.4-kg rat and 70-kg human; water consumption IR_{water} was assumed to be 0.054 L/day in the rat and 2 L/day in the human:

$$IR_{water} = 0.102 \cdot BW^{0.7}$$

Table B-2. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses for Rat Inhalation Study

Species	Strain	Gender	BW (kg)	Route	ED (yr)	EF1 (day/wk)	EF2 (hr/day)	EC (ppm)	EC (mg/m^3)	DM1 (mg hr/L)	HDM/ RDM
Rat	-	male	0.4	I	2	5	7	111.0	400	53079	-
Human	-	-	70	I	2	7	24	35.5	128	53081	0.32

BW=body weight; DM=dose metric; EC exposure concentration; ED=exposure duration, EF=exposure frequency; HDM=human dose metric; hr=hour; kg-kilogram; L=liter; mg=milligram; ppm=parts per million; RDM=rat dose metric; wk=week; yr=year

Exposures in the Kociba et al. (1974) rat drinking water study were simulated as exposures of a 0.4-kg rat to 9.6 mg/kg/day, 24 hours/day, 7 days/week for 2 years. The predicted value for DM1 corresponding to this exposure was 9,610 mg-hour/L (row 1 of Table B-3). Human equivalent doses (HED) were simulated as exposures of a 70 kg human for 24 hours/day, 7 days/week for 2 years (drinking water intake, 2 L/day). The HED that corresponded to a value of DM1 of 9,620 mg-hour/L was 12.9 mg/kg-day (row 2, Table B-3). In the above simulations, both the rat and human drinking water exposures were assumed to be distributed uniformly over a 24-hour period. However, simulations were also run, assuming distribution of the exposure over a 12-hour period (i.e., awake hours when water would be consumed); the value for the HED was 19% lower when a 12-hour/day exposure frequency was assumed (10.5 mg/kg/day) compared to the value obtained when a 24-hour/day exposure frequency was assumed (12.9 mg/kg/day).

Uncertainties in Use of a PBPK Model for Interspecies Extrapolation of 1,4-Dioxane Dosimetry in the inhalation modeling..

The predicted slope of the relationship between exposure concentration and DM1 (and DM2), in humans, is extremely steep in the range of 10–100 ppm; the range in which the dose-equivalence calculations were made for the rat inhalation study (see Figure B-1). Over this range, a 10-fold change in exposure concentration corresponds to a 900-fold change in the dose metric. By contrast, the corresponding change predicted by the rat model is 15-fold. This difference translates into a much higher sensitivity of the dose metric in humans to small changes in assumed exposure concentration, compared to rats. For example, the value of DM1 for a human exposure concentration 5 ppm above the HEC (40 ppm) is 83,320; a 1.57-fold increase above the value that corresponds to the NOAEL (53,081). We have no basis for determining whether such relatively small increases in exposure concentration (14%), above the $NOAEL_{HEC}$ would or would not have adverse consequences.

Table B-3. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses for Rat Drinking Water Study

Species	Strain	Gender	BW (kg)	Route	ED (yr)	EF1 (day/wk)	EF2 (hr/day)	EC (ppm)	Dose (mg/kg/day)	DM1 (mg hr/L)	HDM/ RDM
Rat	-	male	0.4	W	2	7	24	100	9.6	9611	-
Human	-	-	70	W	2	7	24	452	12.9	9611	1.35

BW=body weight; DM=dose metric; EC=exposure concentration; ED=exposure duration; EF=exposure frequency; HDM=human dose metric; hr=hour; kg=kilogram; L=liter; mg=milligram; ppm=parts per million; RDM=rat dose metric; wk=week; yr=year

APPENDIX C. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page C-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered

in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page C-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the

extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

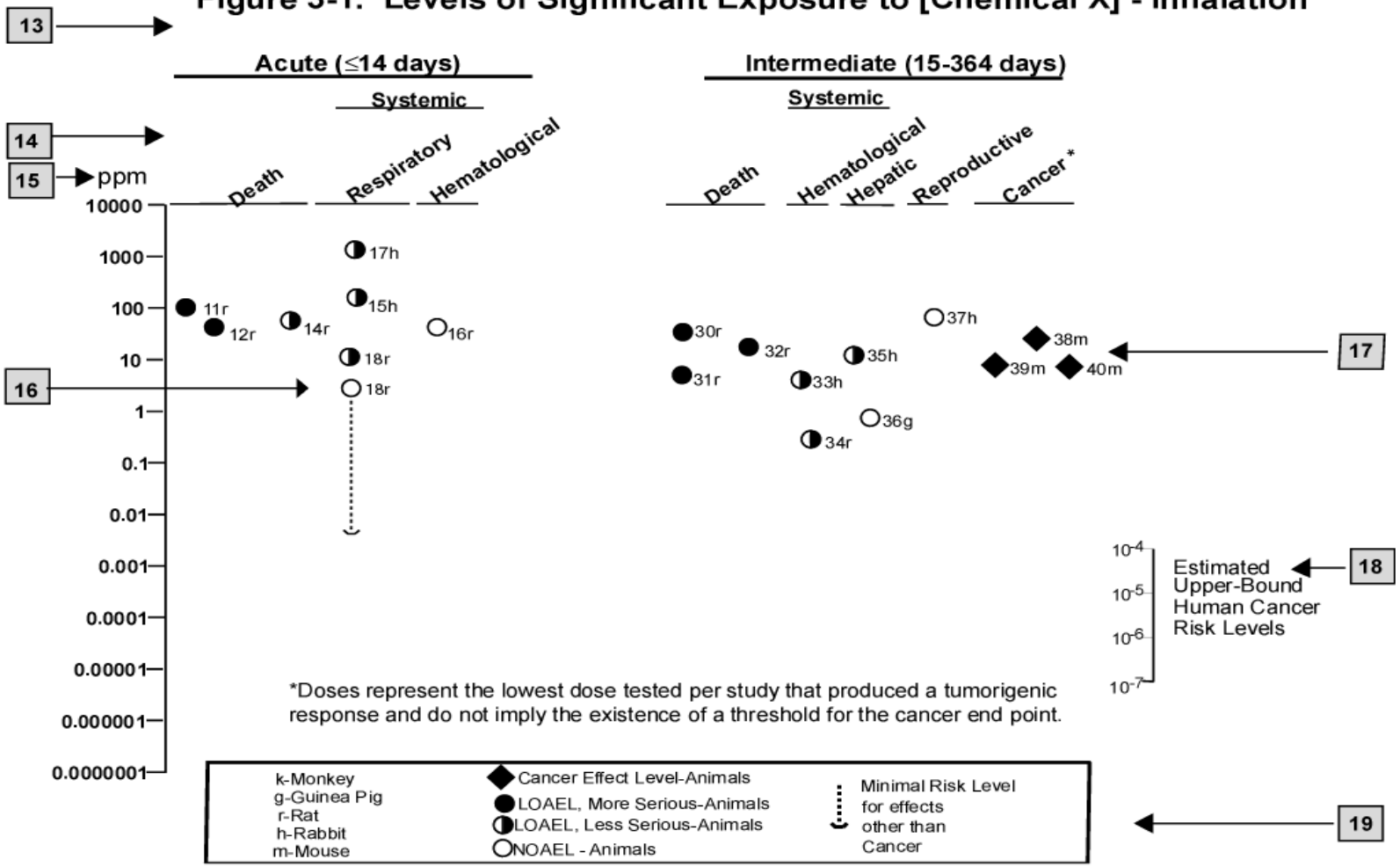
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX E. INDEX